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A CLINICAL STUDY OF THE FREQUENCY OF LEAD, TURPENTINE AND BENZIN POISONING IN FOUR HUNDRED PAINTERS*

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While medical textbooks constantly emphasize the fact that lead is one of the chief agents causing the development of degenerative diseases of the heart, blood vessels, kidneys, nervous system and other organs, there is, however, an accumulation of evidence that in practice this teaching is all too frequently ignored or forgotten. Health officers, particularly in the larger industrial centers, have exceptional opportunity through their study of the causes of death assigned in death certificates, through the reports of hospitals, institutions and private physicians, and especially through inspections of factories and the medical examination of workers, to appraise the importance of lead as a cause of disease. One who makes such studies cannot escape the conclusion that many workers in the great varieties of industries in which lead is employed are injuriously affected by it, but do not seek medical care until they have suffered a severe breakdown; frequently, too, complaints of such persons are treated without being recognized as due to lead poisoning.

This study of painters was undertaken to obtain a more concise idea of the extent to which actively employed workers, most of whom thought themselves in excellent health, gave evidence of damage inflicted by lead paints. The apparent frequency with which tuberculosis in painters, printers and other lead workers who came under the notice of the New York City Department of Health seemed to be associated with exposure to the effects of lead was another reason which led to this study.

For several months, leaders of the various local unions of paints were consulted, and through their efforts an opportunity was obtained to secure the consent of members of the respective labor bodies to be examined. The fear and misgiving that the information derived from this study might serve some other than the announced purpose of framing sanitary measures for safeguarding the health of the workers

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* Since the writing of this report, nearly thirty other painters have been examined with results that are in accord with the findings reported in the study.

had first to be overcome. Through the agency of the officers of the Brotherhood of Painters, 20,000 educational circulars were distributed, in which the dangerous effects of lead, turpentine, benzin and other agents employed by painters were detailed. These served to prepare the way. Painting is a seasonal occupation, and therefore only a relatively small number of examinations could be made during the fall and winter months. When work slackened, and during a period when a strike had been declared, comparatively large numbers of workers presented themselves for examination at the Occupational Clinic of the Division of Industrial Hygiene. Those examined were typical of the entire craft. No effort was made to select special groups according to age or other special distinction. They apparently represented the intelligent and interested members to whom the possibility of improving sanitary conditions appealed, and they came in response to the solicitation of the union leaders. All of these painters were employed in interior painting and decorating, some of them doing wall-paper hanging from time to time. There were no sign painters, carriage, or structural iron work painters among them.

The examinations were made with very few exceptions only by those members of the medical staff of the Occupational Clinic whose medical skill and competency had been carefully ascertained in connection with the other routine work of the clinic. These physicians,[1] to whom grateful acknowledgement is due for painstaking and conscientious work, were first given typewritten instructions prepared by me after study of authoritative works, in which the etiologic factors and the symptomatology of poisoning by the chemical agents used by painters were fully described. The physicians were urged to make the examinations thorough and deliberate, and an average of nearly an hour was given to each case.

Before entering on a description of the trade processes and of the clinical findings obtained in this study, a few words of explanation are necessary as to the reasons for adopting the classification which will be adhered to throughout. Sir Thomas Oliver,[2] gives an appraisal of the relative values of the lead line, basophilia, constipation, colic, anemia, and the presence of lead in the urine. It may here be pointed out that Oliver's estimate of the value of lead in the urine as a diagnostic aid, contrasted with that of Dr. W. Gilman Thompson,[3] is so much at variance with the latter that it may be of interest and value to place the two beside each other.

1. Drs. Charles Pines, Ray Robinson, I. E. Kahn, J. D. Benjamin, Leopold Adams, George Mosher and William Adler.

2. Reprint of lectures delivered before the Royal Institute of Public Health in discussing "What Constitutes Lead Poisoning?" Paul B. Hoeber, New York, 1914, p. 197.

3. The Occupational Diseases.

Thompson says:

> Authorities differ strangely as to the frequency with which traces of lead are demonstrable in the urine in chronic cases. Oliver believes the test to be very positive, and consequently of great value. My own experience corresponds with that of many French and German writers, who find it very infrequently.

Oliver, on the other hand, says:

> I have not found basophilia the help it has been to other physicians. Personally, I rely more on the detection of lead in the urine. Its presence therein is an indication that the metal is in the system and is being eliminated. On the other hand, lead may be found in the urine of lead workers without the men betraying plumbism. These men are on the borderline. Let the elimination be checked, and symptoms at any time may arise. The presence of lead in the urine occupies the same relationship to saturnism as Koch's bacillus does to tuberculosis, Eberth's bacillus to typhoid fever, and Klebs-Loeffler bacillus to diphtheria.

In other words, a person showing lead in the urine is a "carrier" of lead, not in the sense in which that term is ordinarily employed — that he may convey the disease to others — but in the sense that plumbism is latent, and that any disturbance of the balance maintained by the elimination of lead in the urine and feces may precipitate active manifestations of lead poisoning. Or, better still, Oliver[4] compares persons with lead in the urine, but without physical signs, to a person with chronic valvular disease of the heart in whom muscular compensation has not broken down. Through the earnest cooperation of Mr. Halsey Durand, chemist, attached to the Bureau of Food and Drugs of the Department of Health, who made the analysis for lead in the urine, we obtained verification of our diagnosis of plumbism so frequently, that we could not help agreeing with Oliver's conclusions. In this report, therefore, the cases are classified in four general groups as follows:

1. Active or positive cases of lead poisoning. In these, the clinical symptoms speak frankly for lead poisoning. These cases are subdivided into two classes: those in which the diagnosis was made on the basis of clearcut clinical symptoms alone, and those in which in addition to such clinical evidence, lead was found in the urine.

2. Latent, inactive, or laboratory positive cases. In these the symptoms were few, but lead was found in the urine.

3. Doubtful or borderline cases. In these the clinical findings were suggestive.

4. Negative or normal cases.

Further, a word of caution is in place because of the classification here adopted. Because special emphasis is given to the incidence of plumbism, the importance of turpentine and benzin poisoning, and diseases of various organs should not be overlooked.

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4. Bulletin 95, U. S. Bureau of Labor.

CHEMICAL AGENTS AND THE METHODS OF THEIR EMPLOYMENT

Only such facts will be given here as to the kinds of material handled by painters, as may be necessary for a general understanding of the type of poisoning or other disease effects which they might produce. For a thorough and detailed analysis of the methods of work and the character of the chemical agents employed in the painter's trade, the reader is referred to the excellent monograph of Dr. Alice Hamilton.[5] Acknowledgment is here made of the service which this bulletin has given in the preparation of this section of the report.

From a clinical standpoint it is sufficient to know that the following are the chief chemical substances used in the mixing and application of paints: lead, turpentine, linseed oil, benzin or other volatile petroleum products generally spoken of as petroleum spirits, benzol, putty containing lead, amylacetate and wood alcohol.

The lead pigments which are most used are, in the order of their commercial importance:

(*a*). White lead, or basic lead carbonate.
(*b*). Sublimed white lead, or basic lead sulphate.
(*c*). Red lead, or lead oxid (used for painting metal or iron work).
(*d*). Chrome yellow or chrome green (used for painting wagons, carriages, etc.).

While there has been much dispute as to the relative toxic effects of the various forms of lead, it may be accepted as a general rule that lead pigments in whatever form employed tend to induce lead poisoning with slightly varying degrees of rapidity. The colic, constipation, headache, joint and muscular pains, anemia, lead line on the gums, mental and nervous symptoms, especially paralysis or diminished strength of the extremities produced by lead, are too familiar to require more than passing mention. Most lead pigments are now sold mixed with oil, so that the effects of dry lead pigment inhaled or swallowed as dust when mixing paints, are nowadays, and in this country in particular, comparatively negligible. In order to place a sufficiently thick protective covering of paint on a surface, several coats must be applied in succession, especially in work of better quality. Even when applied with care, a varying degree of roughness of surface is left on drying. Before an additional coat is applied, these rough projections and lines must be smoothed down. To effect this, a very considerable amount of sandpapering must be done. *This process liberates large quantities of lead dust and is therefore a most dangerous one.* In Europe, and in Germany in particular, the pumice

5. Hygiene of the Painter's Trade, Bulletin 120, U. S. Department of Labor, Bureau of Labor Statistics.

stone used for smoothing this rough surface is wet with water, and where this is impracticable, sandpaper is wet with one of the cheaper mineral oils having a low flash point.

Before painting is done it is often necessary to remove the old layer of paint or to smooth it down. This may be done by sandpapering, by the use of so-called "varnish removers" containing benzol, wood alcohol or other chemical agents, or, in the case of metallic objects, the paint may be chipped or burned off. The amount of danger in all these processes is in direct ratio to the size of the room or compartment in which the work is being done; to the excellence of its ventilation; and the adequacy of exhaust or other devices for the removal of fumes of lead in burning paint off, and for the removal of benzol fumes, etc., if the latter are used in confined unventilated spaces. Lately, steel or mineral wool has often taken the place of sandpaper. The use of this wool impregnated, respectively, with steel or glass particles, adds to the effects of the lead dust that is liberated, the irritating effect of these metallic or glass particles on the hands, eyes and respiratory organs.

The danger of inhaling or swallowing lead dust generated by sweeping (especially dry sweeping), by the shaking of dirty drop cloths which are used as covers to protect floors and furniture, as well as from the raising of dust by moving or walking about, or from dusty clothing, is quite apparent.

Finally, the danger from hands, mustache, or beard that may be soiled with lead dust and which are not properly cleaned before eating, are too well known to require lengthy description as sources of lead poisoning. Add to this, lack of care in personal cleanliness, alcoholism, and failure to drink milk as a protective agent before and during a day's work, and the chief modes of entrance of lead into the body are apparent.

Linseed oil is used as a vehicle for lead pigment. For years various investigators, and E. C. Bayly in particular, have contended that the lead and linseed form a combination which, in drying, gives off emanations which Bayly has termed "unsaturated aldehyds." These aldehyd emanations cause headache, retching and vomiting, tiredness and often diarrhea. The addition of turpentine to lead and linseed oil increases the amount of the aldehyd. Bayly argues that lead is a slow-acting poison, whereas these symptoms appear rapidly in any individual, following exposure in a room which has been freshly painted. Many differences have arisen as to the part played by lead in this combination. H. E. Armstrong and C. A. Klein hold that the production of volatile emanations is not peculiar to white lead, but is common to all chemical agents which accelerate drying of paint, and they charge turpentine as being the particular cause of these harmful

emanations. Trillat of the Pasteur Institute found, however, that turpentine alone was not responsible for these symptoms, for when he combined turpentine with zinc white instead of white lead, although the amount of turpentine was the same, no symptoms developed, whereas they did appear on exposure to a mixture of turpentine with white lead. The weight of evidence seems to show that white lead, linseed oil and turpentine form a particularly noxious combination.

Henry A. Gardner, writing on behalf of the Paint Manufacturers' Association of the United States, has reported that in drying, paints generate carbon monoxid gas. No conclusive evidence has as yet been brought forth in regard to this theory.

Another process which deserves attention as a source of lead poisoning is the use of white lead putty to fill in cracks, holes and irregularities. This is employed more particularly in painting woodwork where high class work is required. When not pressed for time, putty is used, and after a few days, when it has dried, the entire paint and putty surface is sandpapered.

Turpentine is used to reduce the lead and oil mixture to the desired thinness or consistency; it also assists in the drying of paint. In addition to causing staggering and even unconsciousness, conjunctivitis, skin irritations, nausea and vomiting, von Jaksch has attributed to it headache, dizziness, irritation of the throat and of the bronchial tubes and renal system, dry throat, bronchitis and cough, strangury and bloody urine.

Benzin and the petroleum spirits are highly volatile and are mixed with paints, especially the cheaper ones, when quick drying is desired. Benzin is sometimes used as a thinner in preparing varnish for use on ceilings before kalsomining. The chief symptoms which this group produces, as described by Sommerfeld and R. Fischer, are: headache, vertigo, nausea, vomiting, cough, irregular respiration, weakness of the heart, drowsiness and cold skin; with twitchings and other nervous symptoms on awakening. When these agents are used, it is the practice to shut out currents of freely circulating air because the paint dries too rapidly and produces a streaky effect; painters are therefore exposed to the full effects of the benzin.

Benzol, acetone, wood alcohol and amylacetate are the usual ingredients of varnish and paint-removers employed by painters. Amylacetate is used considerably as a vehicle for bronze pigment. This report will deal little, if at all, with their effects; the subject deserves separate study. The men using these agents complain not only of the effects of the fumes, but suffer from severe skin trouble because of the lack of proper protective gloves.

NUMBER OF CASES OF LEAD POISONING AND TURPENTINE AND BENZIN INTOXICATION

One hundred and sixty-three, a rate of prevalence of 40 per cent., of active cases of lead poisoning, were found among the 402 painters examined in the course of this study. All of these showed definite clinical signs of plumbism; 72, or 44 per cent., of the active cases of lead poisoning among these painters were found to have lead in the urine in addition to clinical evidence. According to Oliver's viewpoint as to latent or potential cases, there were thirty-five, or 8.7 per cent., of the total number examined who were found to have lead in their urine, without manifest clinical signs. In other words, nearly one-half of all the painters examined, or 48.7 per cent., to be more exact, gave evidence of active or latent lead poisoning.

Just as we have found that it is most exceptional for a brass worker suffering from spelter chills to consult a physician, it is likewise very rare that a painter suffering from the effects of turpentine, benzin or one of the other volatile chemicals used as thinners or driers, seeks medical advice on account of their specific effects. They accept the occurrence of the untoward and serious symptoms produced by these poisonous agents with stoic philosophy and complacency, as if they were the most natural circumstances of their trade and rarely consult a physician when overcome. As a result, it is virtually impossible to make any reliable estimate founded on medical observation and study as to the frequency of intoxication produced by these poisonous substances, or to attempt to differentiate from the clinical histories given by these men precisely which one of these volatile chemicals was responsible in any given case for the symptoms described. In this study no attempt has been made, therefore, to distinguish between the effects of turpentine, benzin, wood alcohol, acetone, benzol, etc. At least 70 per cent. of all those examined gave a fairly clear and recognizable history of at least one or many attacks, and 142 painters gave a history of recent severe intoxication, in which several or even all of the following symptoms were noted: a sudden sense of weakness in the legs, irritation of the eyes, difficulty in breathing and dryness and irritation of the throat, cough, headache and dizziness, which in a number of cases was so pronounced that we frequently obtained a history of falls from scaffolding or ladders. In addition, there were often present nausea, vomiting, painful and frequent urination during the day, a few cases of bloody diarrhea, and several others of bloody urine. A number of painters stated, without leading questions, that the urine was subsequently not only very dark, but that it had a very strong and peculiar odor. The verification of these statements must be left to future study. Varnish

removers containing acetone and benzol were reported to have caused severe air-hunger. Most of the painters were emphatic that benzin had caused them more discomfort and illness than all the other volatile agents; its effects seem to be more lasting. A number of very intelligent painters were certain that it had left a feeling of weakness, dizziness and giddiness for one or more days. A few, about seventy in number, who had been at work for varying periods, seemed to enjoy a surprising immunity to the effects of volatile chemicals. Most painters when overcome were quickly relieved when taken into the open air. Some complained that when they went to an open window for fresh air they risked the displeasure of their employer, who charged them with loafing. It was our impression that those suffering from lead poisoning seemed more frequently to suffer from the fumes of these volatile substances. Practically 60 per cent. of the recent cases of turpentine and the related type of intoxications were found among our 163 active and thirty-five latent lead poisoning cases, out of the total of 402 painters studied. Forty-seven of the 142 recent cases had suffered from frequent and moderately painful urination. Occasionally, symptoms that indicated strangury with bloody urine were described. Twenty-three of this group complained of frequent attacks of vertigo. The age groups of the painters who were studied were as shown in Table 1.

TABLE 1.—Lead Poisoning by Age Groups

Age, Years	Active Cases		Latent Cases of Plumbism	Borderline Cases	Negative Cases	Total
	With Lead in Urine	Without Lead in Urine				
20 to 29	12	23	16	18	71	140
30 to 39	30	56	15	15	57	158
40 to 49	18	20	2	8	21	69
50 to 59	10	9	1	3	7	30
60 and over	2	2	1	3	2	10
Total	72	90	35	47	158	402

It will be seen from Table 1 that a comparatively small number survive as active members of the trade after having attained the age of 50 years. Also, 64 per cent. of the active cases of lead poisoning occurred between the ages of 30 and 49 years, whereas seventy-one, or 45 per cent. of all those who apparently were free from symptoms of plumbism, were less than 30 years of age. Taken in connection with the facts that most painters enter the trade before their twentieth

year, and being skilled workers, follow it the rest of their lives, and that of the 109 who were more than 40 years of age, 59 per cent. were found to be suffering from active or latent plumbism, it seems fair to conclude that the action of lead is slow in asserting itself, but that less than half who have passed the age of 40 escape the disease.

Table 2 shows the approximate number of years which those who were examined had spent in the trade.

TABLE 2.—SHOWING APPROXIMATE NUMBER OF YEARS IN THE TRADE

Years at Trade	Active Cases		Latent Cases of Plumbism	Borderline Cases	Negative Cases	Total
	With Lead in Urine	Without Lead in Urine				
1 to 9	10	16	11	20	32	110
10 to 19	28	37	17	14	63	159
20 to 29	15	20	5	8	25	73
30 and over	19	17	2	5	17	54
Total	72	90	35	47	158	402

It will be noted in Table 2 that sixty-three negative cases were engaged at the painter's trade for a period of from ten to nineteen years. On analysis, it was found that most of these were less than twelve years at this work. This table, therefore, seems to emphasize the fact that the heaviest incidence of saturnism is to be found among those who have been painters for ten years or more. Thirty-four per cent. of all those examined who had been painters for ten years or more were active cases of lead poisoning, while if one includes latent cases, the number is increased to 42 per cent. Borderline cases, which are those in whom one or more suggestive symptoms were noted, are not included at any time in this report with the active or latent cases, although there can be little doubt that study extended over a longer period of time would have disclosed evidence that would warrant the diagnosis of plumbism in several of this group.

USE OF ALCOHOL

A satisfactory history with reference to the use of alcohol was obtained in only 304 cases. More than 21 per cent. of those in whom a history as to alcoholic indulgence was obtained were total abstainers, an almost equal number drank excessively, while about 55 per cent. drank very little and only occasionally. We have reason to feel that this information was trustworthy. Alcoholic indulgence, therefore, did not seem in this case to be a marked predisposing factor toward

lead poisoning, as it so frequently has been found. The number of abstainers and of those who drank with great moderation is surprising in view of a number of circumstances that would seem to offer a ready excuse for resort to alcoholic drinks. For example, in buildings that are in process of construction, drinking water is very frequently not provided. Also, in work in occupied apartments, usually of the more expensive sort, inconsiderate housewives, we were told, frequently seem indifferent to the needs of men who are employed to do painting, and appear to regard an effort on the part of the painter to use drinking water or toilet facilities as an unwarranted familiarity or impertinence. It is scarcely to be wondered at that men, under such conditions, should resort to the nearest saloon. Moreover, the parching of the throat caused by turpentine or other volatile substances, produces often a decided craving for something to drink.

TABLE 3.—USE OF ALCOHOL AND LEAD POISONING

	Active Cases		Latent Cases of Plumbism	Borderline Cases	Negative Cases	Total
	With Lead in Urine	Without Lead in Urine				
Abstainers	15	26	1	2	22	66
Moderate users	29	34	16	19	78	176
Excessive users	20	20	6	6	10	62
Total	54	80	23	27	110	304

PRECAUTIONS TAKEN BY PAINTERS AGAINST LEAD POISONING

Under the head of precautions against lead poisoning may be mentioned the drinking of milk before and during work. We found that while forty-five painters were in the habit of regularly taking one glass of milk per day, and eighty-one regularly drank from a pint to a quart per day, the remaining 276 were extremely lax in this particular. A number of these men were accustomed to start the day's work with extremely little or no food for breakfast. Even of those who habitually drank milk, very few took it before starting work. As a class they seemed unfamiliar with the fact that a moderate-sized breakfast and albuminous food (milk in particular), left little free acid in the stomach to act as a solvent of lead dust that might be swallowed during work.

A total of eighteen out of all those examined testified of their own accord that they could not remove the gross particles of lead from their hands before eating lunch on account of the lack of proper washing facilities in the places where they worked, and that they were in

the habit of taking hold of their food with paper to prevent contamination by their fingers. With very few exceptions, washing facilities for use before eating lunch were of the poorest. The use of a nail brush, or of soap and hot water, was very infrequent. A number of the men used turpentine, and a few used benzin as a means of removing paint from their hands. A large number wore mustaches, but few seemed aware of the necessity of special effort to cleanse these, and especially of the need of cleaning their teeth and mouths before meals because of the dangerous dust in which they were working.

Only seventeen of the total number gave a history of chewing gum, and fifteen of chewing tobacco while at work. One hundred and seventy reported that they habitually smoked a pipe, cigars or cigarets while at work. It is difficult to say to what degree these factors may have served as a means of carrying lead into the stomach.

Inquiry was made as to whether special facilities were provided to enable the men to eat their lunches in a room free from the presence of lead dust. It was learned that usually the men were compelled either to eat in the rooms where painting was being done, or, in order to avoid eating in such rooms or in dark, out-of-the-way and often even insanitary cellars of a building, a minority went either to a restaurant or more often to the nearest saloon where a hearty welcome, a fairly clean table, and fairly clean surroundings were to be found.

Many complaints were made that owing to lack of lockers for street clothing, these had frequently to be kept during hours of work where they were thickly covered with paint dust.

SYMPTOMS OF LEAD POISONING

Colic.—Eighty-seven painters, or 51 per cent. of all the active cases of plumbism, gave a history of recent colic. The same complaint was made by three of the latent cases, nine of those who were borderline cases, and eight of the negative cases. Those who complained of colic among the last two groups, in some instances had also other symptoms strikingly suggestive of gastric ulcer or chronic appendiceal inflammation. While a number of the borderline and negative cases had associated symptoms such as backache, constipation, and anemia, which one with an elastic statistical conscience might have been tempted to interpret as cases of plumbism, they were not so classified.

While a number stated that the abdominal pain was localized to the umbilical region, many others described the pain as being of more general distribution. The severity varied greatly in different cases. Some stated that the pain would be repeated often during the day and night but without regularity; others described a definite recurrence of severe cramps at about the same hour each day. Still others described the pain as being of continuous character over a period of

from twenty-four to forty or more hours, with remissions and subsequent return. Twenty-six of the actual cases of plumbism gave a history of repeated attacks of colic during the preceding years, which were accompanied by various degrees of lead neuritis with wrist drop, for which they had to be treated. A surprisingly large number of the positive cases had never sought or received medical advice for this complaint.

Constipation.—One hundred and seventeen, that is 72 per cent. of the active cases of plumbism, or 29 per cent. of all the painters examined, suffered from marked and persistent constipation. In addition, five of the latent cases, nineteen of the borderline cases and forty-three of the negative cases gave the same history. Many of these men stated voluntarily that they would go for days without a bowel movement unless they took a cathartic. Epsom salt seemed to be known particularly to all of them as the cathartic of choice for workers in lead. A small number of the painters were in the habit of taking a daily dose of Epsom salt for short and infrequent periods as a precaution against lead. There is always present the danger that men in this trade will place such complete reliance on the value of Epsom salt as a preventive of lead poisoning as to become totally indifferent to the infinitely more essential measures of dust prevention and cleanliness.

Headache and Other Nervous Symptoms.—Seventy-five — about 46 per cent. — of the active cases, or 19 per cent. of all the painters, complained of frequent and severe headache, usually in the frontal region. The type of headache included under this classification was distinct, according to the history, from the pains in the head which occurred during and immediately after exposure to turpentine, benzin and the petroleum spirits.

Impaired memory and insomnia were mentioned by various painters. No history of encephalopathy, psychosis, or other severe nervous or mental disorders was obtained.

Only three cases of lead paralysis were found in those examined; these were cases of wrist-drop without other involvement. Marked diminution of muscular strength was noted in the right arm thirteen times, in the left arm nine times, and in both arms in forty-six of the active cases. Among the thirty-five latent cases, only one man showed diminished muscular power in the right arm. The latent cases were fairly free from this as also of other characteristic symptoms of plumbism. Very few of the men here studied showed any impairment of muscular power in the lower extremities.

The Lead or Burtonian Line.—The presence of the blue line on the gums, said to be a characteristic symptom of plumbism, was in this experience of little significance. It was found in a total of twenty-

two, or a little less than 14 per cent. of all active cases, in only one of the latent cases, and in a little less than 6 per cent. of all the painters examined. This opinion as to the lack of distinctive value of the lead line has been supported by our subsequent experience in the examination of the gums of many other workers in industries in which large quantities of lead are liberated both as dust and in volatilized condition. Several physicians employed in this vicinity in the medical supervision of large numbers of lead workers share this opinion. Especially in those who are careful as to the cleanliness of their teeth is this symptom infrequently encountered.

Lead in the Urine.—Of the 162 positive or active cases of plumbism, seventy-five, or 46 per cent., gave a definite reaction showing lead in the urine. Of the remaining eighty-seven active cases, in only forty could urine be obtained for this test. These were all negative. Since this test was made in only 115 cases of the group of active lead poisoning cases, in reality, therefore, about 65 per cent. of all positive cases gave the reaction for lead in the urine. The test, in these cases, was therefore one of very considerable diagnostic value.

The reaction as already stated was obtained in thirty-five additional cases, which, in the absence of active symptoms, were therefore classified as cases of latent plumbism.

Thirty-four of the forty-seven borderline cases had the test applied, the chemist in no case being given any intimation of the clinical diagnosis in any of the tests he performed, and of the thirty-four tests, twenty-four gave what he reported as a "suspicious" reaction; sixty-three negative cases had the test applied, and in these only two "suspicious" reactions were reported. All told, the urine of 247 painters was examined for lead. There was a fairly striking correspondence between the results of this test and the clinical diagnosis.

The assistance derived from the examination of urine for the presence of lead in this study was indisputably of great value in diagnosis.

The test is one in which the technic was modified by one of the chemists of the Department of Health, Mr. Durand, and is of such a character that it undoubtedly cannot be readily performed in hospital and private practice. It is on that account not less valuable than other diagnostic laboratory tests which call for special laboratory skill, such as that of the serologist in connection with the Wassermann test, for instance. The technic of the test is here briefly given:

Technic of Lead Test.—After trying the Blyth and several other methods for the determination of lead in the urine, Mr. Durand finally devised a method which gave accurate and fairly delicate results, and yet did away with the boiling over of the tarry mass of urine usually formed in the test, and so made unnecessary that constant watching without which most tests were

spoiled. His method is the following: 200 to 300 c.c. of urine are treated with 5 c.c. of bromin in a porcelain casserole, and evaporated on a hot plate to about 50 c.c. It is then transferred to a platinum dish and evaporated nearly to dryness; 10 c.c. of concentrated nitric acid is then added and the evaporation continued to dryness, the residue again moistened with nitric acid and evaporated to dryness. The residue is then ignited to a low red heat to burn off carbonaceous matter. It is cooled, taken up with 4 to 5 c.c. water and 2 to 3 gm. ammonium carbonate, evaporated to dryness, and the flame played on the dish until the ammonia is driven off. It is then taken up with 15 to 20 c.c. of 10 per cent. acetic acid and boiled and filtered hot into a small test tube. It is then cooled and 1 to 2 drops of colorless ammonium sulphid and a drop of 25 per cent. hydrochloric acid added, and compared with standard samples prepared by adding known amounts of a solution of lead acetate containing 1 gm. of lead per 1,000 c.c. Even less than 0.025 mg. gave a distinct reaction.

Granular or Basophilic Degeneration of Red Blood Cells.—Ever since Ehrlich, and later Grawitz, called attention to the presence of granular degeneration of the red blood cells in cases of plumbism, those who have given much study to this disease have carried on a merry warfare with respect to the frequency with which it occurs in cases of lead poisoning, and with respect to its diagnostic significance. A number of observers, such as Hoffman and Schmidt of Leipsic, Behrend, Hamel, Moritz, Embden and Schönfeld have contended for its value, whereas Teleky and Oliver firmly maintain that it is only infrequently associated with plumbism and that its diagnostic value is of no moment, especially since, as the former asserts, it is present not only in anilin and nitrobenzin poisoning, but in pernicious and other forms of anemia, in malaria, and occasionally even in the blood of healthy persons who have not been in contact with lead. Biondi, in 1906, stated that he had failed to find basophilic red corpuscles in the blood of those suffering from severe lead intoxication.

In the study here reported, the blood of 209 persons was examined for basophilic red cells, with the following results: Of 103 active cases, 13, or a little more than 12 per cent., showed stippling; of 19 latent cases, 5, or barely 21 per cent., were reported positive; of 27 borderline cases, only 4 showed basophilic red cells, and of 60 negative cases, only one was positive. It would therefore appear justifiable on the basis of this study to say that this sign, like the lead line, is of limited practical value.

Anemia.—A marked secondary anemia was found in 86 active cases, or 53 per cent. In 27 of these cases the percentage of hemoglobin was less than 70, as estimated by the Talqvist scale. Among the latent cases 14 patients were found anemic; in the borderline cases 24, and among the negative cases 47. One hundred and seventy-one, or 42 per cent. of all painters reported on in this study, showed this condition. A very large percentage of the men, according to the clinical description of the medical examiners, had an "anxious, worn appearance."

Arteriosclerosis, Heart Affections and Nephritis. — Because of trouble with laboratory and clinic equipment, urinalysis was performed in only 234 cases, and blood pressure readings were recorded in 232 individuals.

Evidence of arteriosclerosis was found in a total of 63 persons, or 26 per cent. of those in whom blood pressure observations were made. Thirty-six of these persons who had a systolic pressure of 150 or more, were active plumbism cases. Of active and latent cases, 44, or slightly more than 39 per cent. of those in whom blood pressure records were made, showed a systolic pressure of 140 or over. The remaining 67 painters, or 61 per cent. of the active and latent cases, had a systolic pressure of 130 or less; this was rather surprising, but it was noted that most of these cases were among those in the youngest age group, and although they had very definite clinical evidence of plumbism, they frequently had a systolic pressure of less than 120. This could possibly be accounted for by the lowering of blood pressure which has been noted in animal experiments as occurring for quite a period of time following exposure to or absorption of lead. The action of lead, as has already been stated, is a slow one, and it is very likely that this low blood pressure is coincident with that period during which fibrotic changes which lead to sclerosis of the vascular system are slowly making headway.

Slightly less than 8.4 per cent. of the painters examined, 20 persons in all, to be exact, showed by the presence of albumin, casts and other physical signs, the presence of chronic interstitial nephritis. This is a smaller number than we had expected to find, but in explanation it should be stated that the urine obtained for examination was frequently a casual specimen. It is possible that on this account a number of diagnoses were missed which repeated examinations of a twenty-four hour specimen would have made possible. Of the twenty cases, sixteen belonged to the group of active plumbism cases.

Eleven of the active cases presented definite heart irregularities and feeble muscular sounds indicative of myocardial changes. Three cases of chronic endocarditis affecting the mitral valves (mitral regurgitation) were noted among the active, three among the latent cases, and three among the borderline cases of plumbism, making nine cases in all; there were five additional cases among the negative group.

Backache.—This symptom was mentioned by ninety-one men, or 56 per cent., of the 162 active cases. The pains were generally localized in the lumbar muscles. To what degree it may be the result of overuse of this particular group of muscles as a result of postural strain in working on ladders, or whether it is due in part at least to the local effect of lead, it is difficult to say. There were five cases of backache in the latent group, thirteen in the borderline cases, and

fifty-two among the negative cases who complained of this symptom. Many of the painters complained of pain in the muscles of the calf and the thigh muscles as well. Dr. Koelsch of Munich, and other German authorities, are disposed to regard all forms of muscular and "rheumatic" pains as due to exposure to extreme cold in painting buildings in the process of construction. The painters in this group were not so exposed.

The Wassermann Reaction.—Much debate has centered about the influence of plumbism on the Wassermann reaction. This question was brought forcibly to the fore in 1914 by Oettinger, Pierre-Louis, Marie and Baron. Cyrus Field[6] reported five out of twelve cases of plumbism in which he obtained a positive Wassermann reaction. Oliver says that in lead patients he only obtained a positive reaction where he had reason to believe that in addition to plumbism there was a syphilitic taint. In this series of cases, of the 162 painters who had active manifestations of plumbism, only ten, or about 8 per cent. of a total of 124 who were tested, gave a positive Wassermann reaction, and in four a doubtful reaction was reported. In each case, however, a history of syphilis or other ground for suspecting syphilis was found. While a positive Wassermann reaction was obtained in ten of the active plumbism cases, the total number of cases belonging to the active group which admitted specific infection was thirteen. Among the other three groups of painters included in this study who were classified with reference to the presence of plumbism, the results were as follows:

In eighteen of the latent plumbism cases which were tested, 2 gave a doubtful Wassermann reaction; of 35 borderline cases the laboratory reported only one positive case; of 99 negative plumbism cases in which blood was obtained, 8 were positive, 2 doubtful and 89 negative. In other words, the test was performed on 272 painters, of whom 120, or 44 per cent., were active cases of plumbism, with a total result of nineteen positive Wassermann reactions and four doubtful reactions.

Miscarriages of Painters' Wives.—It has been repeatedly said that the wives of men who were the subjects of plumbism, were in many instances sterile, or, if they became pregnant, they miscarried; or, finally, if a live child was born, it survived but a short time or was much underdeveloped. No doubt, miscarriages have been frequent among other groups of workers in lead, especially those who, like potters, carry on work at home, making the domestic environment unsafe as regards exposure to lead dust. The marital history obtained from 124 of the active showed that 116 were married, and seven single. Among the wives of these 116 painters, according to the statement of

6. Field, Cyrus: Jour. Am. Med. Assn., 1913, p. 1681.

the latter, there had been a total of 340 pregnancies. The number of children living at the time of the examination was 257; the number of miscarriages was 70, and the number of children who were either stillborn or who died from diseases of childhood, was 13. About 20 per cent. of all pregnancies ended in miscarriage.

Of nineteen latent cases, 17 were married, and 2 single. The wives of these painters had a total of 28 pregnancies, with 19 living children, 6 miscarriages and 3 deaths.

Of 46 borderline cases, 36 were married and 10 single. The wives of these 46 went through a total of 67 pregnancies with 45 living children, 7 miscarriages, and 15 deaths.

Of 153 negative cases in which a marital history was obtained, 53 were single. (The unduly high proportion of single men in this group is indicative of their belonging to the earlier age groups; painters as a class, judged by this experience, marry at a fairly early age.) The wives of the 100 married painters in this group went through a total of 205 pregnancies with 174 living children and 24 miscarriages.

Loss of Weight and Muscular Strength.—This was a surprisingly common complaint. In seventy of the active cases it was very marked, the loss in weight ranging from 8 to 20 pounds in the course of a few years. These seventy cases do not include those men in whom evidence strongly suggestive of pulmonary tuberculosis was obtained.

Digestive Disturbances.—Were frequent among the men. Nausea and vomiting, apart from the digestive upset caused by turpentine, benzin, etc., were emphasized by many in whom no evidence of the toxic effects of lead could be discovered. Fully one third of all painters gave a history of gastric distress, acid eructations, anorexia and nausea, which were especially marked during the season when work was most active. Stimulantism, that is, the resort to alcoholic stimulants, especially by those workers who feel a strong distaste for food, is well recognized and may be looked for where digestive disturbances are frequent. In the experience of the Leipzig Sickness Insurance Fund, and in other German funds where records have been kept, digestive disorders rank high among the causes of morbidity among painters.

Arthralgias and So-Called "Rheumatism."—Pains in various joints were mentioned by 51 painters, or 56 per cent. of those who had signs of active plumbism. Among the 240 latent, borderline and negative cases combined, about 20 per cent. gave a history of joint pains. The joints affected were, in the order of frequency, the shoulder, wrist and hip. While these pains were often characterized by the patient as rheumatic, only exceptionally was a history typical of acute articular rheumatism obtained. The arm which was most used while at work seemed to be most often affected.

Dr. Frank Koelsch[7] of Munich, in 1913, submitted an explanation as to the frequency of chronic and acute articular rheumatism and muscular rheumatism among painters, which does not apply to the special group reported on in this paper. Taking the statistics of the sickness insurance funds of various German cities as a basis, he found that these various forms of rheumatism were caused by work in exterior painting, because of exposure to extremes of weather and to draughts while painting buildings which were in the process of construction. The Leipzig Insurance Fund statistics show that painters were affected by these various forms of articular and muscular rheumatism more frequently than persons employed in all other occupations combined.

While evidence of tonsillitis was rarely obtained in our series of cases, this was given as a cause of illness among painters in many of the cases in the Leipzig insurance funds and elsewhere in Germany; this is referred to because of its possible bearing on joint pains.

Pain in the Chest.—Fifty-five painters belonging to the group of active plumbism cases complained of a dull pain in the chest. This pain had no typical location, being referred to the front of the chest or to the back on either side. As described by the painters, it did not seem to have the character of a pleuritic pain or "stitch," or so-called pleurodynia. There seemed to be so large a degree of similarity, as judged by description, between the character of pains in the back and those about the joints and over the chest that one got the impression that all three types of pain were myalgic in character, and that the joint pains, so-called, were likewise due to pains in the musculature about the joints.

Metallic Taste in Mouth.—Of the 162 active cases of plumbism, thirty, or about 18 per cent., gave a history of having frequently had a distinct metallic taste in the mouth. This sensation did not seem dependent on the presence of the lead line. On the other hand, in all the other types of cases combined, this complaint was made by only four persons.

This concludes the list of essential symptoms elicited in this study with reference to lead poisoning.

PATHOLOGICAL CONDITIONS OF GENERAL INTEREST

Respiratory Affections — Bronchitis and Tuberculosis.—A total of ninety-eight, or nearly one-fourth of all the painters examined, gave a history and physical signs of chronic bronchitis. Fifty-eight of these cases were found among those giving evidence of active plumbism. In other words, 59 per cent. of all cases of chronic bronchitis were

7. Monograph on the Painters' Trade, Hamburg, 1913.

found among the cases of active lead poisoning. In view of the fact that an apparently disproportionately large number of cases of tuberculosis in painters were reported to the Division of Industrial Hygiene by the various Tuberculosis Clinics of the Department of Health during the last two years, the frequency of chronic bronchitis may have distinct significance as a predisposing cause.

Dr. Edgar L. Collis[8] dwells at considerable length on the importance of bronchitis induced by mineral, metallic or other irritant dusts arising in various occupations, as established by a number of students of the subject. He presents a very plausible explanation of the tendency of dusts to produce an antecedent bronchitis which creates a special predisposition to either tuberculosis or to pneumonia. According to this theory, if the dust particles which are inhaled are brittle, insoluble and noncolloidal in structure, they tend to produce tuberculosis; otherwise they predispose to pneumonia. May it not be that interior painters, who are exposed not only to lead dust, which does not appear to be irritating, but to the fumes of turpentine, benzin and other volatile irritants as well, are therefore particularly subject to the development of tuberculosis? At all events, the tendency to emphasize the importance of dust, and to overlook the predisposing influence of other irritant agents should be guarded against. The anemia caused by lead absorption, to which painters are so liable, undoubtedly aggravates the tendency to tuberculous disease of the lungs. In all of our cases of bronchitis, a sputum examination was made, but with negative results.

In this series, in two of the active cases of plumbism the men had moderately advanced pulmonary tuberculosis with tubercle bacilli in the sputum. Twenty-eight had signs in the lungs, and of these, eighteen, or 4.5 per cent. of the total number examined, were reported as showing evidence of an incipient process, without positive sputum. Five of the eighteen incipient cases gave a history of bloody expectoration or marked hemoptysis; all of these men gave a history of marked loss of weight and strength and were anemic, and several gave a history of nightsweats. In only about three or four of these cases could a family history of tuberculosis be elicited. The total of advanced and incipient cases was therefore twenty, or about 5 per cent., and inclusive of suspected cases, 30, or about 7.5 per cent. of those examined.

In the Leipzig, and in other German statistics furnished by Koelsch and several times alluded to, bronchitis was found to be one of the most common complaints, and together with various forms of rheumatism, said to be due to exposure to cold, diseases due to "catching cold" (*Erkaltungskrankheiten*), are said to have constituted 37 per cent. of all cases of sickness reported to the Leipzig Sickness Fund. Just as the cases of rheumatism due to exposure to cold were negli-

8. Milroy Lectures, 1915, Public Health, September, 1915.

gible, because there were practically no exterior painters in our group of 402, so the cases of bronchitis which were found in this study could not be explained as being due to the effects of extreme cold and drafts.

Bronchial Asthma.—Seventeen cases of bronchial asthma were found in this series; eight of these were cases of active plumbism.

Skin Diseases.—Acne, especially on the back and face, and chromophytosis were very frequent. In this report, however, interest is centered in those forms of dermatitis which might be held to be the result of the paints and their ingredients. Twenty-three marked cases of occupational dermatitis of eczematous type, showing as a rule squamous patches, were found. These affected the fingers and hands principally, occasionally the face. Slight lesions were ignored. In a number of cases marked calosities were recorded over the anterior tibial border of the legs, where pressure had been made against the rungs of stepladders. Although a number of painters complained that following the use of turpentine, and varnish removers more particularly, they suffered from a severe inflammation of the hands, which was accompanied by a cracking of the skin and a considerable amount of bleeding, those conditions were not observed in the course of our examinations. This was in all likelihood due to the fact that the men came under our notice during a period when they were without work, and when such lesions would have had ample opportunity to heal.

Teeth.—Ninety painters had a fairly marked pyorrhea alveolaris, and 104 showed marked decay of the teeth and lack of care, making a total of 194, or about 48 per cent. of all who were examined.

Visual Defect.—Only marked defects of vision were noted. Fifty-one such cases were found. Ophthalmoscopic examinations were not made.

Nose and Throat Defects.—Chronic pharyngitis was found in 127 painters. Hypertrophic rhinitis was reported in twenty-eight cases, and marked deviation of the septum in 147 painters. In only fifteen was marked hypertrophy of tonsillar tissue found.

Varicose Veins and Flat Feet.—Forty-two men had varicose veins and seventy-two showed marked flat foot.

Inguinal hernia was present in six cases, while a number who had previously suffered from this condition had been cured by operation.

REPORT ON INVESTIGATION OF HOME CONDITIONS OF ONE HUNDRED FIFTEEN PAINTERS

The criticism is frequently made that tuberculosis, anemia, malnutrition, nervous disorders and other abnormal conditions of health are wrongly attributed to the influence of occupation, when in reality,

insanitary home environment, lack of food, and domestic worries may be responsible for such conditions. In order to obtain definite data with respect to home conditions and their possible influence on health, nurses attached to the Occupational Clinic staff were instructed to visit the homes of all in this series of painters who lived within a radius of about four or five miles of the clinic. The visits were made during the day time. A number of painters had moved to other quarters during the interval between their examination at the clinic and the visit of the nurse; in still other cases the homes were found closed on several occasions, and they were not revisited. In all, 115 painters' homes were investigated. Speaking generally, it may be said that the sanitary conditions were found to be good. Cleanliness, freedom from overcrowding, good ventilation and lighting, a sufficient and varied diet and absence of alcoholic excesses among the members of the families were the general rule. For those who may be interested in the details of the conditions reported in the homes, the accompanying tabulation is given (Table 4).

RECOMMENDATIONS FOR THE PREVENTION OF OCCUPATIONAL DISEASES AMONG PAINTERS

In view of the high mortality and morbidity rates among painters, compared with all others engaged in industry, as determined by authorities in England, France, Germany, the United States and elsewhere, it would seem urgently necessary that strong measures be taken by public health agencies for the protection of workers in this particular trade.

Summerfeld in Berlin, Koelsch in Munich, F. L. Hoffman in this country, Is. P. De Rooys of Holland, and Legge of England, have amply demonstrated in their statistical reports and studies the preponderance of disease and the heightened death rate among painters. Dr. John B. Andrews reviewed the deaths from lead poisoning that occurred in the State of New York during 1909 and 1910, and of sixty deaths that were officially reported to the State Department of Labor, he showed that forty-five occurred among painters, thirty-seven of whom were house painters. It scarcely needs more argument than has been presented by those cited above to bring home the full significance of a vigorous campaign to improve the conditions which are undermining the health and hastening the death of thousands of painters.

The remedial measures that suggest themselves may be divided into two general classes: first, public health measures; second, personal hygiene.

Public Health Activities.—Public health authorities can never cope with the problem of prevention in any particular field unless full infor-

TABLE 4.—Home Conditions of 115 Painters

	Active Lead Cases	Latent Cases	Borderline Cases	Negative Cases	Total
Number of homes visited	23	43	10	39	115
Number of homes of married men	10	35	9	22	96
Number of homes of single men	4	6	1	5	16
Number of widowers	0	3	0	2	5
Wages per week:					
$12 to $15	2	0	0	2	4
15 to 20	8	7	0	7	22
20 to 25	11	16	0	25	52
Information refused	5	2	0	0	7
Over $25	0	18	9	0	27
Length of employment per annum:					
6 to 7 months	3	7	0	6	16
About 8 months	11	17	3	11	42
About 9 months	1	13	5	10	29
10 months or over	4	2	0	3	9
Not stated	4	4	0	9	17
Number of children in family:					
None	9	26	6	19	60
One	5	5	1	5	16
Two	2	7	1	2	12
Three or more	7	5	2	13	27
Number of children contributing to income:					
One in family	1	2	0	0	3
Two in family	0	5	1	2	8
Three or more	1	0	0	2	3
Number of boarders per family:					
One	2	0	0	1	3
Two	0	2	0	1	3
Three	1	0	0	1	2
Average weekly income from all sources:					
$15 or less	2	7	0	1	10
Up to $20	7	17	7	14	45
Up to $25	6	15	0	15	36
$25 or over	2	1	0	2	5
No information	3	0	0	0	3
Rental per month:					
$15 or less	5	25	0	23	59
$15 to $20	7	8	2	6	23
$20 to $25	5	1	2	4	12
$25 or over	2	1	0	2	5
Janitors, living rent free	3	0	0	0	3
Food. Quality:					
Good	19	38	10	28	95
Fair	1	8	0	5	14
Poor	3	1	0	2	6
Quantity:					
Sufficient	18	30	10	31	98
Insufficient	2	3	0	0	5
Indefinitely stated	3	4	0	5	12
Variety:					
Good	15	27	10	33	85
Fair	4	0	0	2	6
Poor	3	10	0	4	17
Alcohol consumed in the home:					
Excessive	0	0	0	1	1
Moderate	13	16	9	5	43
None	7	23	5	12	47
Indefinitely stated	3	0	0	11	14
General cleanliness:					
Good	19	32	10	32	93
Fair	3	8	0	3	14
Poor	1	1	0	3	5

TABLE 4.—HOME CONDITIONS OF 115 PATIENTS—(*Continued*)

	Active Lead Cases	Latent Cases	Borderline Cases	Negative Cases	Total
Ventilation:					
Good	16	31	9	27	83
Fair	2	7	1	7	17
Poor	5	4	0	6	15
Lighting:					
Good	17	35	9	2	63
Fair	3	4	1	7	15
Poor	3	3	0	2	8
Number of rooms per family:					
Three	3	14	0	11	28
Four	14	16	6	14	50
Five or more	4	12	3	8	27
Number of bedrooms:					
One per family	7	2	0	9	18
Two per family	6	27	5	17	55
Three or more	3	10	5	10	33
Number of persons per bedroom:					
One	3	1	1	12	17
Two	15	34	8	19	76
Three	4	5	1	4	14

As regards a number of items which are included in this tabulation, definite statements were frequently not obtainable from the person who was interviewed; for this reason, such information was frequently omitted from the tabulation of data just given.

mation is obtained as to the extent and prevalence of a given disease and of all circumstances which predispose to its occurrence. Just exactly as it is essential for success in the prevention of typhoid fever to have complete reports of all cases occurring in the community, in order to be able to ascertain what possible sources of infection may have caused any particular group of cases, so it is essential, above all things else, not only that physicians shall be held legally responsible for the reporting of all cases of lead poisoning that come to their professional notice, but employers, large and small, should be required by law to keep a register of all cases of occupational diseases and of accidents resulting from work, which occur among their employees. If, by a system of factory inspection and adequate penalties, such a law were enforced, the frequency of such diseases would become fully known to the public health authorities. The particular processes or employments in which such diseases occurred could be definitely ascertained and the proper measures could then be instituted for the elimination of the factors causing such diseases.

Aside from such a general measure of control, the following specific provisions should be enacted:

1. The mixing of dry lead pigments with oil or paints, while not a frequent source of danger, should not be permitted except when proper provision for the efficient removal of lead dust that may be generated in the process, has been made.

2. Dry sandpapering should be prohibited, the use of pumice stone and water, or sandpaper moistened with one of the cheap mineral oils having a low flash point, should be made mandatory.

3. When chipping of paint, or the removal of paint by the use of acetone, wood alcohol, benzine, benzol or other volatile poisonous agent is employed, protective clothes and gloves of suitable character, kept in good repair, should be provided by the employer. If this wok is done in confined or enclosed spaces, adequate means for ventilation should be provided. The enforced use of gloves in painting, and also in removing paint, would be an ideal measure of prevention, because it is through soiled fingers more largely than through any other source that poison is introduced into the body.

An educational campaign would be necessary among painters to prevail on them to use such gloves if their provision was made mandatory. In an inquiry that was conducted among a limited number of painters, it was found that about 40 per cent. did not take kindly to the idea of wearing gloves, though this is entirely practicable for most forms of work.

Lockers or other adequate provision for the protection of street clothes from contamination by lead dust should be made mandatory on all jobs, small or big, whether done in a shop or carried on in apartments. Overalls should be provided; keeping them in good repair and clean is a matter of personal hygiene for which special educational effort would be required. Free access to toilets should be guaranteed to every employee, whether work is to be carried on in buildings which are in process of construction, or elsewhere. Washing facilities and especially hot water, nail brush, soap and towels should be provided by every employer. Many painters who today use turpentine for this purpose because of lack of hot water and other necessities, would gladly avail themselves of such facilities; and that minority which is indifferent to the use of this most important protective measure could be induced to adopt the habit through educational effort.

Lunch-room provision in a place apart from shops or apartments in which painting is done or in which lead pigments are mixed, should be provided on all jobs.

Drop cloths should be frequently changed or washed.

The Substitution of Zinc for Lead.—For many years a bitter and confusing debate has been waging between those who advocate the substitution of zinc oxid for white lead, and the champions of the latter paint-pigment. Numerous experiments have been carried on in England and in France particularly, to settle the dispute as to whether zinc oxid is practical for use, especially in interior work, because it is the exposure to lead dust in interior painting that is the most harmful element in the painter's work. In France, certain public buildings have for some years been painted with a zinc oxid paint containing no lead, and have been exposed to various influences of climate and air contamination, with apparently satisfactory results. Had it not been for the present war, a law passed by the French legislature would have gone into effect in 1915 to prohibit the use of white lead in

interior painting. In England, the opinion of many master painters seemed equally divided as to the practical value of substitution of zinc oxid for white lead.

Professor Ladd of North Dakota, in a letter to the writer in 1916, did not share the faith of those who thought the substitution of zinc oxid was feasible, and insisted that personal hygiene was the chief element in the elimination of lead poisoning among painters.

A room in one of the clinics in the Department of Health was painted a year and a half ago with a paint containing zinc oxid without any lead ingredient of any character, and while it has not been exposed to fumes or other influences which affect the wearing qualities of paint, it seems to have given good service. It would be manifestly unfair on the basis of this limited personal experience to venture any opinion on this moot question which has engaged the study of the foremost technical experts. One may, however, express the hope that either zinc oxid may be found feasible and useful as a substitute for white lead, in order to diminish the unusually high rate of sickness and death among painters, or else that manufacturers of white lead or other lead pigments, and employers of labor, will join with public health authorities in an energetic and sincere effort to employ all educational and all other agencies for the safegurding of the health of the many thousands of workers who are employed in this trade. At present there is no estimate available of the total number of painters in the United States. In the German sickness insurance funds in 1914 it was estimated that over 168,000 men were employed in Germany as house painters; this was exclusive of employers and foremen. This gives some idea of the enormous number whose health and welfare are involved in this trade in every country. If one were to include the numerous industries in which painting is an important essential as a part of general manufacture, the number of painters would undoubtedly be very greatly increased.

Labeling of poisonous agents.—Every manufacturer of paint in North Dakota, and those who wish to sell paint products in North Dakota, are made responsible for a definite statement on a label as to poisonous ingredients which the paint mixtures may contain. This law is highly commendable and should be adopted elsewhere. Moreover, the clear labeling of all mixtures placed in the hands of employees by employers should be required, so that all poisonous ingredients may be known; and such label should contain a proper warning as to the dangers of such mixture and the method of preventing poisonous effects; and such warning, furthermore, should be printed in the language familiar to the particular group of workers who may handle such paint.

The German law provides for many of these safeguards and is clear and explicit about the provision of temporary working sheds for the protection of clothing and for use as lunch rooms. In connection with regulations for the protection of painters during lunch periods, it is important to recognize that the painters who receive a mere half hour for lunch and who are not allowed extra time for washing will be subjected to an overwhelming temptation to omit this most important preventive measure. It should therefore be made mandatory that at least five minutes should be allowed from working time for the use of washing facilities before eating lunch.

Compensation for occupational diseases and for occupational lead poisoning in particular, will do more to safeguard the health and lives of workers than any other single legal or hygienic measure. It should not be delayed.

Personal Hygiene.—Personal hygiene is so intimately connected with some of the measures that have already been considered, that it has been unavoidable to make passing mention of them in the course of the recommendations made under the preceding heads. It is most essential, as Richard Miller has pointed out, that workers be made to realize that they are exposed to unusual danger, and that the man who is poor in health and has low powers of resistance, will, in all likelihood, be much more readily susceptible to lead poisoning, to tuberculosis, and other diseases peculiar to painters than one who is well nourished. So dangerous is this trade, and so important is personal hygiene, that a robust and powerful man entering this trade, unless he exercises due care as regards his person, will succumb more readily than a painter having low powers of resistance who exercises extreme care as regards personal cleanliness and general hygiene. Washing of the face, mouth, hands and mustache, particularly before eating, stands as the foremost protection to be taken by painters. By washing is not meant a mere perfunctory exercise, but a thorough cleansing of the hands with hot water, nail brush and soap. It would be manifestly impossible to urge this on painters unless the law compelled the provision of these facilities.

Eating before going to work is a valuable and necessary precaution. Lead seems to be much more readily absorbed from an empty stomach than from one which contains milk or other food. Milk is especially valuable for the purpose and should be taken during the day.

The use of alcohol subjects persons to a greater risk from lead poisoning and makes them more readily susceptible to the effects of turpentine, benzin and other volatile agents.

Painters should be warned against dry sweeping. A moistening agent should be employed wherever this is necessary, and while it has been found practically impossible to induce painters to employ respira-

tors, they should be urged to wear same, especially when dust is unavoidably raised in any process.

Smoking.—Smoking, which is regarded as a most innocent habit by the majority of workmen, has a peculiar danger to the painter. It is not the effect of the nicotin or tobacco which is warned against, but it is the unavoidable placing of lead dust in the mouth through the handling of cigars or cigarets or pipes with lead-stained fingers, or through placing tobacco or chewing gum into the mouth with such soiled fingers, that constitutes the grave danger.

When any painter is compelled to use a paint material containing benzin, turpentine or other volatile poison in a confined or enclosed space, special means for ventilation should be provided, or if this is impossible, such employees should work on short shifts, being permitted to leave their work for a few minutes to go to a window for relief from the suffocating effects of such dangerous fumes. Those painters doing interior work or working in buildings which are in the process of construction, should be particularly careful to wear adequate protective clothing to protect themselves from the effects of draughts and colds.

SPECIAL COOPERATIVE INVESTIGATION OF PAINTING DONE FOR THE CITY OF NEW YORK

Through the courtesy of Dr. Royal Meeker, Commissioner of the Bureau of Labor Statistics of the State Department of Labor, Dr. Alice Hamilton, who has been widely recognized as an investigator of occupational diseases, became interested in making a study, together with the writer, of the conditions under which painting on public property was done in the City of New York. Complaints had been frequently received, and from varied sources, to the effect that many of the conditions which were responsible for disease among painters in various occupations, also existed in connection with the painting of much of the public property of the City of New York. A number of the public bath houses, public lavatories, detention quarters for prisoners and other buildings were inspected by Dr. Alice Hamilton, who made a special visit for the purpose in the winter of 1916, and who, in some of these visits, was accompanied by the writer.

In brief, it was found that practically all of the conditions which obtained in the painters' trade and are encountered in private enterprise, were also present in connction with the painting of these buildings. There were corners or closets in many of the buildings in which, no doubt, painting without special devices for ventilation was bound to cause benzin poisoning. Varnish removers were also in use in a good many instances, exactly as they were in connection with private work. In prison quarters, it was found that the prisoners, who had not had

previous experience in this work, were given painting, sandpapering, scraping, or other work to do which created considerable amounts of lead dust, without having received proper instruction as to methods of protecting themselves against lead poisoning.

The character of the work varied with different types of buildings that were inspected. Again and again, information was brought to us by various painters that the work done under contract for the city in connection with school buildings was often of a character in which large quantities of inferior paint were employed, and in connection with which a larger amount of thinners and driers were employed than with other grades of paint. This, so far as our investigations went, was apparently true in some cases. We were also informed that at various periods the spray method of painting was used in connection with the painting of park benches, although it was impossible at the time of our inspection to verify these facts from personal observation. It is well recognized that the spray method of painting, unless surrounded by safeguards of unusually excellent character, is one of the most dangerous methods and may produce disease as the result of exposure to lead spray and to fumes of turpentine and benzin. The essential fact brought out by the investigation made jointly by Dr. Alice Hamilton and me was that industrial hygienic supervision is a most important and useful function to serve, not only in connection with private business, but equally in the multitude of industrial activities of a large city. The strictures made in connection with painting done for the city do not indicate a lessened regard for human welfare on the part of those who are conducting this work, but rather they reflect an indifferent and unenlightened attitude with respect to the health protection of painters throughout all American cities.

139 Center Street.

THE PRACTICAL IDENTIFICATION OF ENDOTHELIAL LEUKOCYTES IN DIFFERENTIAL BLOOD COUNTING

FOURTH REPORT OF STUDIES ON THE MONONUCLEAR CELLS OF THE BLOOD *

F. A. McJUNKIN, M.D., AND ALICE CHARLTON, M.A.
MILWAUKEE

A method for the identification of endothelial leukocytes in the peripheral blood has been reported by one of us.[1] This method, as was pointed out in its description, is not well adapted to routine work on account of the impossibility of bringing all cells into contact with the carbon particles of the suspension employed to determine the phagocytic properties of the leukocytes. The purpose of this paper is to record the application to blood films of an indophenol staining reaction which brings out characteristic cytoplasmic granules in the endothelial leukocytes.

Leukocytes Granule Stain.—To apply the stain, a blood film made in the usual way on a 22-mm. square coverglass is covered for one half minute with 5 drops of an alphanaphthol-methyl-violet solution in order to fix the preparation; the alcoholic stain is then diluted with an equal amount of distilled water, and the dilute stain allowed to act for five minutes. The preparation is washed with water, dried with filter paper, counterstained for two or three minutes with 0.01 per cent. basic fuchsin (Grübler), washed, dried in the air, and mounted in balsam.

To prepare the alphanaphthol-methyl-violet solution, add 0.2 gm. alphanaphthol (Merck reagent), 0.015 gm. methyl violet 5 B. (Grübler) and 0.2 c.c. hydrogen peroxid to 100 c.c. of warm 80 per cent. alcohol (made from absolute alcohol). The hydrogen peroxid used should contain approximately 3 per cent by weight of the gas as determined by titration with decinormal potassium permanganate.

Reaction of the Blood Cells to the Stain.—Nuclei and cytoplasm are colored red, except the cytoplasmic granules in neutrophils, eosinophils and endothelial leukocytes, which are blue. The granules of basophils are of a distinctive red color. The granules of the eosinophils are large and the central portion appears unstained so that these granules have a very characteristic ringlike appearance not seen in the granules of other leukocytes. The platelets take the red stain faintly; the erythrocytes are pink.

Since the red cytoplasm of lymphocytes is entirely free from bluish granules, the only differentiation requiring discussion is that between

* Submitted for publication June 3, 1918.

* From the Pathological Laboratory of the Marquette University School of Medicine.

1. McJunkin, F. A.: THE ARCHIVES INT. MED., 1918, **21,** 57.

the neutrophils and endothelial leukocytes. That these two cells have an entirely different origin has been shown elsewhere by one of us.[2]

The character of the granules of the endothelial leukocytes and the relationship between granules and nucleus distinguish them from polymorphonuclear neutrophils. Of these two points, the first is of greater importance. The granules of the endothelial leukocytes are discrete and the cytoplasm is distinctly seen between them, while the neutrophilic granules are so thickly placed that little of the cytoplasm can be seen. The neutrophilic granules are larger and more regular in shape than those of the endothelial leukocytes (Plate, A, B, C). In pathologic blood in which mononuclear myeloblastic cells (neutrophilic myelocytes) are present the character of the granules assumes a greater significance. However, since the granules of neutrophilic myelocytes and of the so-called metamyelocytes are even more prominent than those in the polymorphonuclear neutrophils, there is no chance of confusing myelocytes and endothelial leukocytes, although both are mononuclear. The differential character of the endothelial leukocyte is the presence of blue granules in a mononuclear cell. Although the nucleus of this leukocyte frequently has a broken outline, it does not consist of pyknotic nuclear masses connected by filaments. The reason that endothelial leukocytes cannot be identified in films stained with a polychrome blood stain is that some of these cells, such as the one shown in B in the plate, are entirely devoid of granulation and cannot, therefore, be distinguished from lymphocytes when they approach these cells in size.

Endothelial leukocytes after incubation with carbon suspensions according to the method previously referred to[1] contain carbon. That the carbon-containing mononuclear leukocytes (Plate, D, E, F) react typically to the stain is proof that the cells under consideration in this and previous reports are one and the same.

Since some of the endothelial leukocytes contain no granules when stained with polychrome blood stains, and since they approach lymphocytes in size and shape, reported increases in the nonlymphocytic mononuclear leukocytes must be accepted with qualifications. Increases in the so-called "transitional" leukocytes have been reported in typhoid fever, Hodgkin's disease, malaria, and other conditions by various observers. F. A. Evans[3] found 40 per cent. of this variety of leukocyte in a case of secondary syphilis under treatment with salvarsan.

The authors have examined the blood in four cases of syphilis under treatment with preparations of arsphenamin (arsenobenzol brand) with the results recorded in the following paragraphs.

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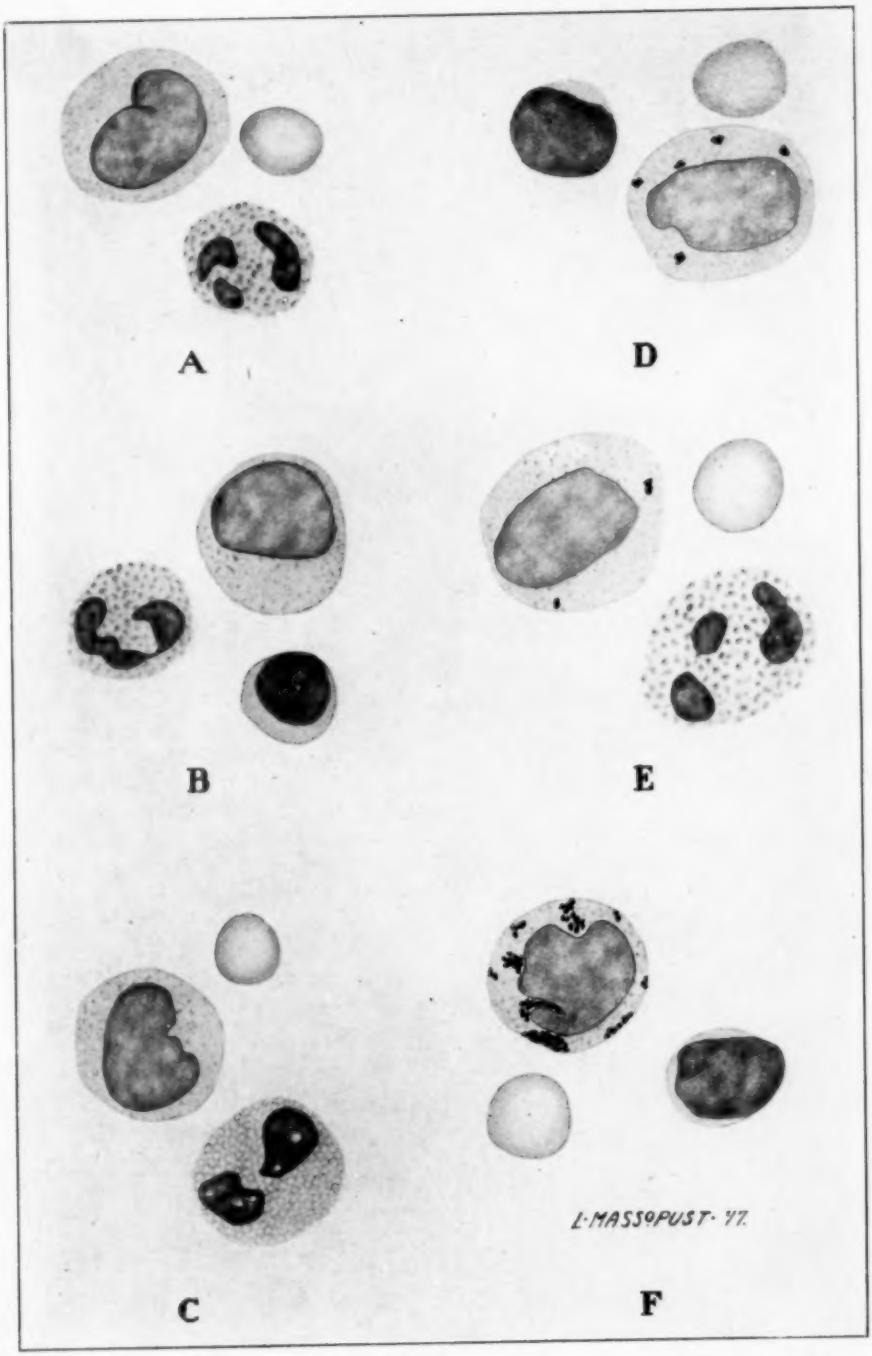
2 McJunkin, F. A.: Am. Jour. Anat., 1918. In press.

3. Evans, F. A.: THE ARCHIVES INT. MED., 1916, **17**, 1.


A
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REPORT OF CASES

CASE 1.—H. S., man, aged 21; hereditary syphilis; Wassermann +++. Feb. 6 to March 22, 1918, five doses arsphenamin and five doses salicylate of mercury; last dose of arsphenamin seven days before examination of the blood. The blood examination showed 6,950 leukocytes per cubic millimeter, with 7.2 per cent. endothelial leukocytes, 60.6 neutrophils, 28.7 lymphocytes, 2.6 eosinophils, and 0.9 basophils.

CASE 2.—E. S., man, aged 25; secondary syphilis; Wassermann ++++. Two doses of arsphenamin; last dose twelve days before examination of the blood. Blood examination showed 9,650 leukocytes with 6.1 per cent. endothelial leukocytes, 56 neutrophils, 34.8 lymphocytes, 2.3 eosinophils, and 0.8 basophils.

CASE 3.—J. A., man, aged 40; lesion on the tongue; Wassermann ++++. Feb. 8 to April 5, 1918, received four doses of arsphenamin; last dose ten days before examination of the blood. The blood examination shows 6,700 leukocytes with 8.35 per cent. endothelial leukocytes, 51 neutrophils, 37.24 lymphocytes, 2.02 eosinophils, and 1.39 basophils.

CASE 4.—E. W., man, aged 29; syphilis ten years previously; at the time of examination there were difficulties in the movements of the left leg and arm; Wassermann "doubtful." April 12, 19 and 26, and May 3 and 10, he received intravenous injections of arsphenamin. The following percentages of endothelial leukocytes were present: April 10, 5.65; April 11, 3.35; April 13, 3.24; April 15, 4.83; April 17, 3.3; April 20, 5.05; April 23, 4.9; April 25, 4.6; April 27, 5.3; April 30, 7; May 4, 6.38; May 7, 6.03; May 11, 4.23; May 15, 4.5. The number of leukocytes varied between 6,200 and 10,600.

In thirty-four differential counts made on the blood of normal adults the average percentage of endothelial leukocytes was found to be 5 per cent.; an average of these leukocytes on the seventeen counts made on the four cases of syphilis receiving arsphenamin is 5.3 per cent. The percentages are based on counts of from 1,000 to 2,000 leukocytes. It would seem, therefore, that increases in this variety of cell are not produced by the intravenous injection of arsphenamin.

CONCLUSIONS

The endothelial leukocytes of the peripheral blood can be stained differentially. That the stain is specific is shown by staining blood in which this variety of leukocyte is characterized by ingested carbon.

EXPLANATION OF PLATE

Drawn with camera lucida and oil-immersion objective.

A, B, and C are cell groups from normal blood stained with leukocytic granule stain: A, endothelial leukocyte, neutrophil and erythrocyte; B, endothelial leukocyte, neutrophil and lymphocyte. If it were not for the distinct blue granules in the endothelial leukocyte, it would be difficult or impossible to differentiate it from some of the lymphocytes; C, endothelial leukocyte, erythrocyte, and eosinophil. Note the ringlike appearance of the eosinophilic granules.

D, E, and F are cell groups from normal blood incubated at 37.5 C. with a carbon suspension; films stained with leukocytic granule stain: D, lymphocyte, erythrocyte and endothelial leukocyte containing carbon; E, erythrocyte, neutrophil, and endothelial leukocyte containing particles of carbon; F, erythrocyte, lymphocyte, and endothelial leukocyte containing numerous carbon particles that have been ingested by phagocytosis.

I. THE BLOOD SUGAR IN THYROID AND OTHER ENDOCRINE DISEASES

THE SIGNIFICANCE OF HYPOGLYCEMIA AND THE DELAYED BLOOD SUGAR CURVE *

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NEW YORK

It is generally recognized that the thyroid and other endocrine glands exert an influence on carbohydrate metabolism, but a clear understanding of this function has not as yet been reached. Experimental studies of this subject were accordingly undertaken and are reported in this article. They demonstrate that following the abolition of thyroid function there ensues (1) hypoglycemia and (2) a tendency to delayed removal of glucose from the blood; that is, a delayed blood sugar tolerance curve. Clinical studies on hypoglycemia and the blood sugar tolerance were also made in a series of thyroid and other cases. This paper presents a detailed account of these observations which emphas[illegible] the value of blood sugar estimations in the study and diagnosis [illegible] iseases.

I. Experimental Hypoglycemia and the Delayed Blood Sugar Curve.—Previous studies on the effect of thyroidectomy on carbohydrate metabolism have led to contradictory results. Falkenberg,[1] Rahel Hirsch,[2] also Underhill and Saiki[3] have reported diminished tolerance to carbohydrates after thyroidectomy. Eppinger, Falta and Rudinger failed to obtain similar results. Subsequently these authors,[4] and also McCurdy[5] reported an increased tolerance for sugar after thyroidectomy, with preservation of the parathyroids, in all or in part. Hunter[6] observed increased sugar tolerance after thyroidectomy in sheep. The chief cause of these discrepancies is the extreme difficulty of performing thyroidectomy in dogs without injury to the parathyroids, which minute organs very probably influence carbohydrate metabolism differently from the thyroid glands. In the work of all of these authors, the tolerance studies have been confined to an exam-

* Submitted for publication March 22, 1918.

* From the Montefiore Hospital, New York City. For a preliminary report of this research see Soc. Exper. Biol. and Med., 1917, **14,** 99.

1. Falkenberg, W.: Cong. f. inn. Med., 1891, **10,** 502.
2. Hirsch, R.: Ztschr. f. exper. Path. u. Therap., 1908-1909, **5,** 233.
3. Underhill, F. P., and Saiki, T.: Jour. Biol. Chem., 1908, **5,** 225.
4. Eppinger, H., Falta, W., and Rudinger, C.: Ztschr. f. klin. Med., 1909, **67,** 380.
5. McCurdy, J.: Jour. Exper. Med., 1909, **11,** 798.
6. Hunter, A.: Quart. Jour. Exper. Physiol., 1914, **8,** 1.

ination for sugar in the urine. Schulze,[7] however, observed a fall in the blood sugar of patients after thyroidectomy, while in others in whom hyperthyroid symptoms were present a rise in the blood sugar occurred after the operation. McLean[8] reports a decreased ability of the heart to utilize glucose after thyroidectomy.

1. *Experimental Methods.*—It was therefore decided to study the effect of thyroidectomy in animals, avoiding the uncertainty of former investigations by (1) employment of careful surgical technic, (2) by tolerance studies made with the aid of a delicate blood sugar tolerance test, and (3) by using a sufficient number of animals to render the results of value.

The sugar tolerance was tested by a specially devised modification of a similar procedure recently worked out by us[9] for human subjects. The technic employed was as follows:

Technic.—Healthy dogs were placed in metabolic cages and the normal rise in the blood sugar observed after the administration of a definite amount of glucose dissolved in water (6.5 gm. glucose per kilogram of animal's weight in 40 per cent. solution. No other fluid was given on experimental days). The blood sugar was determined immediately before the ingestion of the glucose then in hourly periods thereafter until the normal level was reattained. The urine was also carefully collected and the twenty-four-hour specimen tested for glucose. On five animals thyroidectomy was performed by Prof. J. E. Sweet of the University of Pennsylvania, who favored us with his unusual operative skill. In all cases the thyroid glands were carefully removed in toto and the parathyroids, as noted in the protocols, isolated with their blood supply and preserved.

Not all the parathyroid glands described for dogs were isolated in each case, and it is possible that a certain amount of parathyroid tissue was removed with the thyroids. Underhill and Hildilch[10] have shown that two parathyroids can carry out the vital function of these endocrine glands, and in our dogs two parathyroids at least were isolated in every case and preserved with their blood supply, as shown in the protocols. That these glands remained in good condition was demonstrated later at necropsy. Recovery from the thyroidectomy operation took place in each instance without any indication of tetany. The metabolism studies were not resumed for at least ten days after the operation. For these reasons it is believed that in the animals studied, trauma or parathyroid injury may be reasonably excluded. The wounds healed aseptically in each instance, the dogs developing no immediate symptoms which could be ascribed to the operation. Later

7. Schulze, F.: Beitr. z. Chir., 1912-1913, **82,** 207.
8. McLean, F. C.: Ztschr. f. Physiol., 1913-1914, **27,** 582.
9. Janney, N. W., and Isaacson, V. I.: Proc. Soc. Exper. Biol and Med., Nov. 21, 1917. Jour. Am. Med. Assn., 1918, **70,** 1131.
10. Underhill, F. P., and Hildilch, W. W.: Am. Jour. Physiol., 1909-1910, **25,** 66.

some of the animals displayed a tendency to sluggishness and obesity, also an increased susceptibility to infections. The effect of the removal of the thyroid glands on the fasting blood sugar was then determined, together with the influence of the operation on the utilization of glucose fed in the same quantities and under the same conditions as before.

TABLE 1.—Blood Sugar Tests on Normal Dogs*

Dog	Before Glucose Ingestion, Per Cent.	After Glucose Ingestion		
		1 Hour, Per Cent.	2 Hours, Per Cent.	3 Hours, Per Cent.
1	0.082	0.119	0.108	†
2	0.074‡	0.095	0.120	0.075
3	0.099	0.150	0.136	0.102
4	0.102	0.154	0.135	0.113
5	0.080	0.066	0.081	.....
6	0.111	0.140	0.140	0.113

* Three other normal dog tests are reported in the following table.
† Blood could not be obtained.
‡ Hypoglycemia of unknown cause in a healthy dog. The curve, however, is perfectly normal.

TABLE 2.—Blood Sugar Tests Before and After Thyroidectomy (Dogs)

Dog	Operation	Before Glucose Ingestion, Per Cent.	After Glucose Ingestion					
			1 Hr., Per Cent.	2 Hr., Per Cent.	3 Hr., Per Cent.	4 Hr., Per Cent.	5 Hr., Per Cent.	6 Hr., Per Cent.
1	After	0.072	0.087	0.092	0.095	0.088	0.085	.....
2	After	0.063	0.070	0.075	.....	0.075	0.065	.....
	After	0.076 ?	0.145	0.135	0.130	0.120	0.084	0.063
3	Before	0.080	0.130	0.100	0.085	.....	.....	.....
	After	0.081	0.121	0.109	0.100	0.097	0.079	.....
4	Before	0.097	0.138	0.111	0.106	.....	.....	.....
	After	0.083	0.105	0.103	.....	0.093	0.082	.....
5	Before	0.100	0.164	0.115	.....	0.080 ?	.....	.....
	After	0.063	0.097	0.102	0.083	0.066	.....	.....

2. *Experimental Results.*—A marked *hypoglycemia* was found in every case to appear after thyroidectomy, the average decrease in the blood sugar being about 26 per cent. In one instance, Dog 3, the blood sugar was found not to have fallen below the pre-operative level. This dog, however, for some unknown cause, showed a hypoglycemia before operation. The experiment does not stand, therefore, in contradistinction to the others.

Another interesting fact elicited is that following thyroidectomy the feeding of glucose produced a greater *percentile* rise in the blood sugar over the fasting level than occurred when the gland was intact. The actual values representing the *amount of sugar* in the blood following

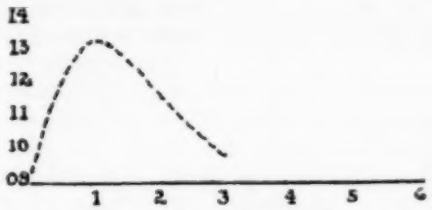

Chart 1.—Schema showing the effect of glucose ingestion on the blood sugar. The average curve of nine normal dogs. In Charts 1 to 6 the horizontal line represents the hours and the vertical line indicates the blood sugar in per cent. after thyroidectomy; broken line before thyroidectomy.

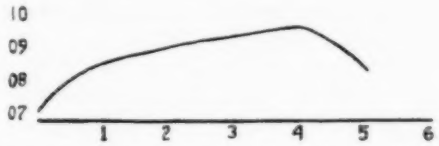

Chart 2.—Blood sugar curve of Dog 1. Solid lines indicate the curve after thyroidectomy.

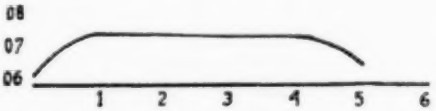

Chart 3.—Blood sugar curve of Dog 2 after thyroidectomy.

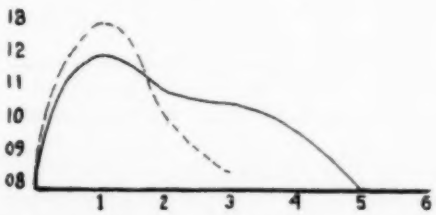

Chart 4.—Blood sugar curves of Dog 3 before and after thyroidectomy.

the glucose ingestion were, however, not so large in the postoperative experiments, this being due to the hypoglycemia.

These results are clearly shown in the schemata which also demonstate that, aside from the hypoglycemia ingested sugar after reach-

ing the circulation is much more slowly removed than it was previous to thyroidectomy. It is apparent that glucose fed under conditions identical with those before operation required four or five hours rather than two or three hours to vanish from the circulation.

3. *Discussion of Results of the Thyroidectomy Experiments.*—These results are of importance from several standpoints. First, they clearly demonstrate the very intimate relation of the thyroid

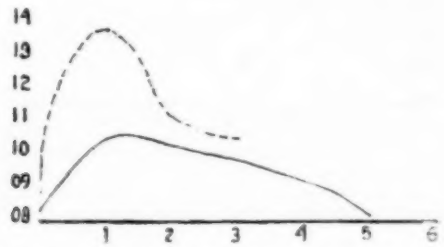

Chart 5.—Blood sugar curves of Dog 4 before and after thyroidectomy.

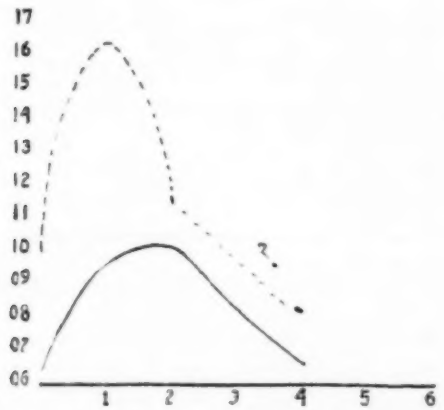

Chart 6.—Blood sugar curves of Dog 5 before and after thyroidectomy.

to carbohydrate metabolism, as the thyroid evidently functions to maintain the blood sugar at its normal level. Secondly, they show that hypoglycemia follows abolition of the function of an endocrine gland. It is very important to determine whether other ductless glands have the same effect on carbohydrate metabolism. Apparently the suprarenals function likewise, for hypoglycemia has been reported following epinephrectomy.[11] The hypoglycemia in this instance has, how-

11. Bierry, H., and Malloizel, L.: Compt. rend. Soc. Biol., 1908, **65,** 232.

ever, been criticized by Frank and Isaac[12] as being an antemortem phenomenon, because death ensued shortly. Failure of the pituitary function may also lead to hypoglycemia, as will be mentioned later.

It is evident from a study of the protocols and curves that in addition to hypoglycemia a prolonged sugar curve was a result of thyroidectomy in every case. This is of extreme interest, as it seems clearly to indicate that the normal action of the thyroid is to aid in the proper assimilation of carbohydrate.

Reasoning from *a priori* grounds one would not expect delayed blood glucose assimilation coincident with hypoglycemia, for it could be argued that the less sugar in the blood the more readily should glucose be removed from it. It may of course seem rather paradoxical to speak of an increased tolerance existing in conditions in which a delayed blood sugar curve is present. In such a blood condition as just described, urinary sugar tolerance is, however, increased. The deciding factor is the hypoglycemia. It must be remembered that the tendency to delayed assimilation is never so great as to lead to hyperglycemia and glycosuria. Thus, the highest point in the assimilation blood sugar curve of a cretin before treatment was 0.109 per cent. It seems, then, justifiable to regard the hypoglycemia as a possible *cause* for the increased sugar tolerance of these conditions, as determined by the presence or absence of sugar in the urine.

It is possible that the thyroid exerts its effect on carbohydrate metabolism in part, at least, through an influence on the liver. Parhon,[13] also Cramer and Krause[14] and Kuriyama[15] in careful experiments have demonstrated that the feeding of small amounts of thyroid tissue causes the liver glycogen to disappear. The explanation suggested by Cramer and Krause that the thyroid decreases the glycogenetic function of the liver seems, however, inadequate, for if this were true one should expect the blood glucose markedly to increase rather than decrease after thyroidectomy. The questions here involved are, however, too intricate for lucid discussion at present.

It is of great importance to determine whether the delayed blood glucose curve observed after thyroidectomy is really due to the loss of thyroid function or whether it is due to other causes. Such a cause might be sluggishness in alimentary absorption, as is held by Magnus-Levy.[16] However, neither this investigator nor, subsequently, others presented any definite experimental proof substantiating this view. We

12. Frank, E., and Isaac, S.: Ztschr. f. exper. Path. u. Therap., 1909-1910, **7,** 326.
13. Parhon, M.: Jour. physiol. e. d. Path. gén., 1913, **15,** 75.
14. Cramer, W., and Krause, R. A.: Proc. Royal Soc., 1912-1913, **86,** 550.
15. Kuriyama, S.: Jour. Biol. Chem., 1918, **33,** 193.
16. Magnus-Levy, A., von Noorden's "Handbuch d. Path. des Stoffwechsels," Berlin, 1907, p. 335.

have, therefore subjected the matter to the following test: Former experiments by Janney[17] demonstrated that large amounts of glucose are formed in the organism from the proteins of meat. The sugar excretion following the ingestion of meat by completely diabetic dogs rose and fell nearly synchronously with the excretion of nitrogen resulting from the break-down of the protein constituents of meat. Carbohydrates are known to be formed from proteins under normal conditions; also, the nitrogen of ingested meat is rapidly excreted. Therefore, if we follow the rate of excretion of the nitrogen of meat fed to fasting animals we are able to get an indirect but clear insight into the alimentary rate of absorption of the carbohydrate and protein metabolites of the meat ingested. A weighed mixed diet, including meat, was accordingly fed to a fasting dog before and after thyroidectomy. Nitrogen determinations were made on urinary specimens collected by catheterization at two hourly intervals.

TABLE 3.—URINARY NITROGEN EXCRETION CURVE

Operation	Day	Weight, Kg.	Period	Nitrogen Fed, Gm.	Volume Urine, C.c.	Total Nitrogen, Gm.
Before	1	10.0	24 hr.	5.83	*	*
	2	9.9	24 hr.	5.83	400	5.35
	3	9.9	24 hr.	5.83	428	5.30
	4	9.8	24 hr.	5.83	392	5.96
	3	....	8:30-11:30	....	60	0.82
			11:30- 2:30	....	200	1.22
			2:30- 5:30	....	68	1.02
			5:30- 8:30	....	35	0.70
			8:30- 8:30	....	65	1.54
After	1	9.2	24 hr.	5.83	340	5.74
	2	9.1	24 hr.	5.83	387	5.97
	3	9.05	24 hr.	5.83	320	5.75
	2	....	9:20-12:20	....	22	0.82
			12:20- 3:20	....	120	1.37
			3:20- 6:20	....	60	1.10
			6:20- 9:20	....	65	0.83
			9:20- 9:20	....	120	1.85

Table 3 demonstrates that the urinary nitrogen curve in the athyroid condition is practically the same as before thyroidectomy. For the reasons developed we may hence conclude that alimental absorption is unimpaired in such cretin animals. On the basis of these experiments the delay in the blood sugar utilization curve in our experiments is evidently not to be explained by a sluggish alimentary absorption.

17. Janney, N. W.: Jour. Biol. Chem., 1915, **20**, 321.

II. Hypoglycemia and the Blood Sugar Curve in Clinical Conditions.—In order properly to define hypoglycemia it is necessary to recognize the normal variations in the blood sugar level. In attempting to do this one must bear in mind that the analytic methods for determining the small amounts of sugar present in the blood have only recently been placed on an exact basis. Many observations on the blood glucose in the past are therefore of dubious value. This is particularly true for low values which were formerly reported so frequently, the reason usually being that glycolysis with consequent loss of sugar readily takes place in blood withdrawn from the body. It is probable that on this account wide variations in the blood sugar have been reported for normal individuals even in recent blood sugar studies. During the past few years a large number of blood glucose determinations have been made not only by the writer (N. W. J.) and

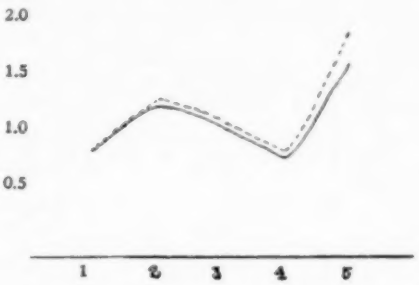

Chart 7.—Urinary nitrogen excretion curve before and after thyroidectomy. Solid line indicates before thyroidectomy; broken line after thyroidectomy. The horizontal line represents three-hour periods, and the vertical line indicates the nitrogen in grams.

his co-workers, but also in a number of other laboratories. Although the values obtained are too scattered for proper presentation at present, yet without doubt the great majority in normals range from about 0.085 per cent. to 0.11 per cent. We thus come to the original opinion of Bang,[18] whose exhaustive studies on blood sugar caused him to place the normal value at 0.10 per cent., this value being established on the basis of an accurate analytical technic. Occasionally lower values are met with in apparently normal subjects, but in our experience subsequent examinations in such cases have revealed a normal level for the blood glucose. We therefore consider hypoglycemia to be present when values permanently below 0.085 per cent. are obtained.

1. *Clinical Conditions Showing Hypoglycemia.*—Hypoglycemia is much less frequently met with than hyperglycemia. In view of experi-

18. Bang, I.: Der Blutzucker, Wiesbaden, 1913.

TABLE 4.—Decreased Blood Sugar Tolerance in Endocrine Diseases

Patient	Disease	Treatment	Before Glucose Ingestion, Mg.	After Glucose Ingestion					Urinary Glucose, Gm.
				1 Hr. Mg.	2 Hr. Mg.	3 Hr. Mg.	4 Hr. Mg.	5 Hr. Mg.	
Y. K.	Cretin	Before	65	109	85	85	75	65	
		After	104	164	116	106			
M. S.	Myxedema	.....	96	...	115	88			
A. S.	Hypothyroidism	.....	103	...	150	125	...	...	Faint trace
B. G.	Dysthyroidism	.....	110	180	150	120			
E. T.	Exophthalmic goiter	Before	100 97	184	...	105	92	...	0.75
		After	70	107	72	...	...	...	0
J. W.	Exophthalmic goiter	Before	99 98	192	151	120	112	...	6.13
		After	122	224	164	130	...	...	4.90
J. H.	Exophthalmic goiter	Before	70 52	122	117	91	87	...	4.34
		After	98	138	114	91	...	...	0
M. F.	Exophthalmic goiter	.....	70	115	107	91	87	74	0
M. S.	Exophthalmic goiter	.....	88	110	108	86	...	...	Faint trace
J. D.	Exophthalmic goiter	.....	108	181	130	110	...	...	
R. S.	Acromegaly	.....	134	234	197	140	...	...	0
I. B.	Acromegaly; muscular dystrophy	.....	66	127	95	90	63	...	0

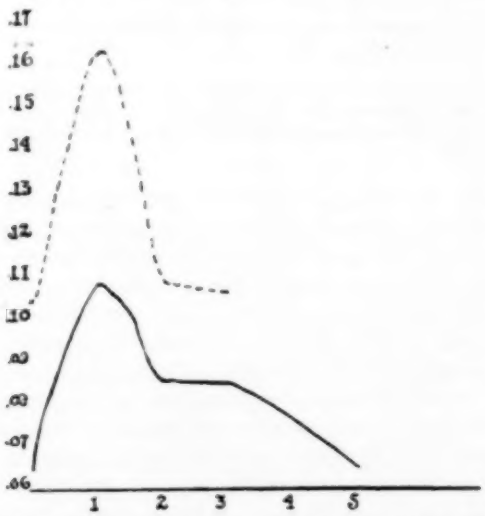

Chart 8.—Blood glucose curve in a cretin, Y. K., before and after treatment. The horizontal line represents the hours, the vertical line represents the blood sugar per cent., the solid curve line indicates before treatment and the broken line after treatment.

mental observations of a low blood sugar level after removal ot the thyroid gland, blood sugar determinations in myxedema and cretinism become of considerable interest. Myxedema cases showing a distinct hypoglycemia have been reported by Geyelin,[19] the sugar values being

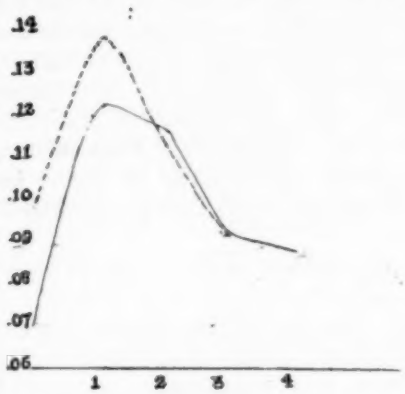

Chart 9.—Blood glucose curve in exophthalmic goiter. The lines and figures of the chart have the same explanation as those of Chart 8.

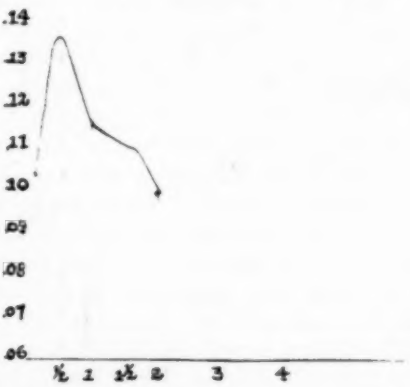

Chart 10.—This scheme represents the average blood glucose curve of seventeen normal persons and is reproduced on the same scale for comparison. The blood sugar test was made precisely as in the other human experiments here reported.

0.053 per cent. and 0.068 per cent. Two slight cases of myxedema and hypothyroidism in our series showed normal blood sugar values, but a prolonged tolerance curve.

19. Geyelin, H. R.: The Archives Int. Med., 1915, **16,** 975.

Our cretin showed 65 and 70 mg. of sugar per 100 c.c. of blood before thyroid was administered. Her case is of unusual interest for the blood glucose curve before treatment was markedly delayed just as was the curve in thyroidectomized animals. After proper thyroid medication practically normal values were obtained for both the fasting level of the blood glucose and for the assimilation curve (see protocols). The high glucose tolerance of Knöpfelmacher's case[20] of cretinism which, after thyroid medication, decreased to normal, finds an adequate explanation in our findings. Similiar cases are known in the literature. Various cases of untreated myxedema[20] have been reported showing small amounts of glucose in the urine. In such instances the decrease in tolerance has probably developed before the hypoglycemia.

We have recently obtained other new data on hypoglycemia[21] which was reported at the 1917 meeting of the American Medical Association in a paper on the endocrine origin of muscular dystrophy. This disease, because of certain clinical and pathologic findings which cannot be entered into here, is most probably to be regarded as a symptom complex resulting from failure of proper function of one or more endocrine glands. The blood sugar and various phases of metabolism were studied by us in a representative series of nine dystrophy cases. In every individual distinct hypoglycemia was detected. It is also a striking fact that the majority of the cases showed the same peculiar delay in the blood sugar assimilation curve as was observed in animals after thyroidectomy. Indeed, practically the same metabolic picture was observed as we had been able to produce experimentally by removing the thyroid gland. Thyroid lesions have been reported in several cases of muscular dystrophy. We do not hold the view, however, on this account that muscular dystrophy is necessarily due to thyroid involvement, as hypoglycemia can result from dysfunction of various endocrine organs. Moreover, there is evidence that the pituitary and possibly the pineal gland may also be at fault in this myopathy. Our results seem sufficient, however, definitely to rank muscular dystrophy among the endocrine diseases. Hypoglycemia has been observed by McCrudden and Sargent[22] in another case of muscular dystrophy. Addison's disease is known to be associated with hypoglycemia, Porges[23] reporting 0.033 per cent. sugar in the blood of one

20. Knöpfelmacher, W.: Wien. klin. Wchnschr., 1904, **17,** 244.

21. Janney, N. W., Goodhart, S. P., and Isaacson, V. I.: Tr. Am. Med. Assn., June, 1917; THE ARCHIVES INT. MED., 1918, **21,** 188.

22. McCrudden, F. H., and Sargent, C. S.: THE ARCHIVES INT. MED., 1916, **17,** 465.

23. Porges, O.: Pfluger's Arch. f. d. ges. Physiol., 1912, **154,** 311.

patient. Bernstein,[24] also Japanese observers,[24] likewise observed a low blood level in this disease. Janney[25] has observed it in a third case, the values obtained being 0.082 and 0.075 in the fasting condition. In hypopituitarism Cushing and Jacobson found hypoglycemia to be present. In view of these clinical findings, persistent hypoglycemia may be fairly regarded as a symptom of hypofunction of the ductless glands. It is very probable that as observations with good analytical methods multiply there will be increasing significance attached by clinicians to the presence of a low fasting blood sugar level.

2. *The Blood Sugar Curve in Exophthalmic Goiter.*—It has long been known that occasionaly glycosuria is present in this condition; also that there is usually a decreased power to assimilate carbohydrate. More definite information was afforded by Geyelin, who found hyperglycemia in 90 per cent. of moderate and severe cases. In mild cases the blood sugar was found to be normal. A slower return to the normal level after sugar ingestion was noted and attention was called to the diagnostic value. Recently Cummings and Piness[26] reported a delay in the time taken for the blood sugar to return to its former level after sugar was eaten. Forsbach and Severin[27] have also reported a delay in the return of the blood sugar to its former level in tolerance tests on patients with exophthalmic goiter.

The distinctive feature exhibited by our protocols is a very early tendency for a delay to appear in the blood sugar assimilation curve. Thus, Case M. S., which was clinically characterized by but a very mild degree of hyperthyroidism, slight thyroid enlargement, a pulse rate of 90, and mild nervous symptoms, showed a normal fasting value for the blood sugar and only an hour lengthening of the curve. The blood sugar tolerance test is evidently of more importance than the fasting blood sugar level in exophthalmic goiter, for Case J. H. exhibited a marked prolongation of the curve though the fasting value was originally below normal. We observed a tendency for greater prolongation of the blood sugar tolerance curve in the severer cases. As far as present observations go, the results of the blood sugar tolerance test seem an early and definite sign of thyroid disease, and serve as an indication of the severity of the underlying metabolic disturbance. It is significant that the three exophthalmic goiter patients whose blood was again studied after improvement under hygienic and

24. Bernstein, S.: Berl. klin. Wchnschr., 1911, **48,** 1794; Sakoguchi, K., Tatsuya, K., and Kinyosai, O.: Mitt. a. d. med. Fakult. d. k. Univ. z. Tokyo, 1915, **14,** 3.

25. Janney, N. W.: Unpublished observation.

26. Cummings, R., and Piness, G.: The Archives Int. Med., 1917, **19,** 777.

27. Forschbach and Severin: Arch. f. exper. Path. u. Pharmacol., 1914, **75,** 168.

dietetic treatment exhibited a tendency for the blood glucose curve to shorten and approach the normal (see protocols).

3. *The Blood Sugar Curve in Hypophysial Disease.*—The first case of acromegaly studied by us showed all the usual characteristics of this disease. Enlargement of the lower facial bones and extremities was marked. Bodily strength was fairly well retained. The blood sugar was definitely increased in amount and the tolerance curve markedly delayed. It is remarkable that the blood sugar in this instance, in the absence of nephritis, attained the value of 0.254 per cent. in the tolerance test without the appearance of glycosuria. The tolerance is usually decreased in acromegaly, glycosuria being reported in 35 per cent. of cases by Borchardt[28] in a series of 176 cases. It is exceedingly interesting that a few cases are known in which glycosuria has been succeeded by a marked increase in toderance.[29] In these instances, just as in myxedema following hyperthyroidism, hypofunction of the hypophysis is to be suspected. Such a case is that of I. R. (see protocol) which has already been reported in detail in a previous study.[21] Here the symptoms of muscular dystrophy were superimposed on those of acromegaly, giving a very interesting syndrome in which the degenerative features predominated. In contradistinction to the first case, R. S., here marked hypoglycemia is present. The blood sugar curve is delayed in both instances as the protocols show, but glycosuria was absent in both cases.

Diagnostic Value of Hypoglycemia. — The experimental studies reported in this article definitely demonstrate that hypoglycemia is a sign of hypofunction of the endocrine glands, the thyroid being taken as an example of these organs. The clinical occurrence of low blood sugar values in diseases representing hypofunctional conditions of ductless glands (cretinism, myxedema, Addison's disease, hypopituitarism) unmistakably indicates the general significance of this symptom. Just how great the diagnostic importance of hypoglycemia will become must be awaited as a result of the accumulation of future studies. It must be remembered that hypoglycemia is occasionally met with in apparently normal individuals (see the foregoing), but this is transitory as far as the few observations recorded permit one to judge. The hypoglycemia in hypofunctional endocrine conditions is permanent. As the metabolic processes are in general more fundamental indications of the actual underlying condition of a given disease than are the more variable and frequently confusingly complex clinical symptoms, the writers are inclined, in doubtful cases, to put consider-

28. Borchardt, L.: Ztschr. f. klin. Med., 1908, **66,** 332.

29. Goetsch, E., Cushing, H., and Jacobson, C.: Bull. Johns Hopkins Hosp., 1911, **22,** 165.

able weight on the state of the blood sugar. Thus it has been found an aid in the diagnosis of pluriglandular cases presenting a complex and vague symptomatology. Another group in which blood sugar determinations are helpful are those exhibiting a mixture of hyperthyroid and hypothyroid symptoms, attention to which has been called by Bertine.[30] In the presence of hypoglycemia the hypothyroid side of the case may be regarded as predominating and thyroid treatment is indicated. Hyperglycemia is, on the other hand, a contraindication to thyroid treatment. It must be remembered, however, that some of these obscure cases present a normal blood glucose, which may mean that they have reached midway in their transition from a hyper- to a hypo- condition. One must also bear in mind that thyroid medication used in excess may produce hyperglycemia and even glycosuria.

In difficult cases the blood sugar tolerance test as previously described by us[9] may be carried out. A prolonged blood sugar curve is an additional indication of endocrine involvement. It is to be remembered that a delayed blood glucose curve is found in both hypothyroid and hyperthyroid conditions.

CONCLUSIONS

Experimental proof that hypoglycemia results from hypo-endocrine function was obtained in the case of the thyroid gland, where hypoglycemia regularly developed after thyroidectomy. Explanation is thus afforded for the low blood sugar value observed in myxedema, cretinism, Addison's disease and pituitary disease and other less clearly defined endocrine conditions such as muscular dystrophy.

The increased tolerance to glucose as determined by testing the urine in such diseases of the ductless glands is probably to be best explained as due to the hypoglycemia present in these conditions.

Delay in the assimilation of glucose from the blood was found to follow thyroidectomy in animals by employment of a blood glucose tolerance test. The same change was demonstrated in cretinism, exophthalmic goiter, and hypophysial disease. Determination of the fasting blood sugar value and the blood glucose tolerance test are useful in the diagnosis of endocrine diseases.

NOTE: After the completion of this article there was published the report of Hamman and Hirschman (THE ARCHIVES INT. MED., 1917, **20,** 761) of similar studies which corroborate independently many of our observations. This important contribution has unfortunately appeared too late to be quoted in our text.

We desire to acknowledge the assistance rendered by Miss Maude Hays in the dietetic and analytical work of this research.

30. Bertine, E.: Med. Rec., New York, 1916, **90.**

II. THE INFLUENCE OF THYROIDECTOMY AND THYROID DISEASES ON PROTEIN METABOLITES *

N. W. JANNEY, M.D., AND V. I. ISAACSON, B.S.
NEW YORK

I. INTRODUCTION

The endocrine glands undoubtedly play an important rôle in controlling metabolic processes. This field fascinatingly invites research study, both on accoumt of its high scientific interest and its clinical importance. For some time past we have been investigating the influence of the thyroid gland on metabolism. The problems investigated have comprehended the relation of the thyroid to (1) carbohydrate metabolism, (2) protein metabolism and (3) thyroid therapy.

In the present article the influence of the thyroid on certain aspects of protein metabolism are considered. Although it has been known for a long time that the administration of thyroid preparations stimulates protein catabolism, and conversely that the abolition of thyroid function diminishes tissue breakdown, still our knowledge of the influence of the thyroid on specific nitrogen metabolites such as ammonia, creatinin and the purins has remained rudimentary. Better information is here very desirable, since if one could, for example, trace the control of creatinin and purin metabolism to the thyroid or other ductless glands, the curtain obscuring an understanding of the causes of various myopathies and even the gouty diathesis might be raised.

A study of the influence of the thyroid, taken as a type of the endocrine organs, on the nitrogen metabolism is therefore of considerable importance. This problem has been attacked by us from two chief directions. First, we endeavored to learn more about thyroid function by estimating the nitrogenous constituents in the urine of animals before thyroidectomy, and then observing the changes occurring after the operation; that is, the metabolism of experimental athyroidism. Second, the metabolism of experimental hyperthyroidism was studied by following the chemical urinary changes after injecting an overdose of the isolated thyroid hormone. Third, supplemental studies were made in cretinism and exophthalmic goiter, as types of hypothyroidism and hyperthyroidism.

II. METABOLISM IN EXPERIMENTAL ATHYROIDISM

1. *The Experimental Plan.*—This consisted in making a complete quantitative study, that is, partition, of the nitrogenous substances of

* Submitted for publication April 22, 1918.
* From the Montefiore Home and Hospital.

the urine of fasting dogs and repeating this examination after removal of the thyroid glands. Before and after the operation, the sparing action of glucose on protein metabolism was simultaneously followed for purposes to be mentioned later. The same precautions to insure accuracy in these metabolic experiments were taken as have been described in preceding researches by one of us and his co-workers.[1]

In view of the fact that the same experimental subjects have been used in a recent investigation[2] on the effect of thyroidectomy on the blood sugar, it seems unnecessary to repeat the details here. It may, however, be stated that considerable care was exercised throughout in removing the thyroids and that no parathyroid tetany or other disturbing factors developed. The animals before and after the operation remained in excellent general condition, which fact gives added reliability to the results.

During the experimental periods, both before and after the operation, the dogs received as diet nothing but 40 c.c. water per kilogram of body weight, except on the sugar days, when 6.5 gm. glucose for every kilogram of the animal's weight were dissolved in this amount of water and administered by mouth. By this means the results of the metabolic study before and after thyroidectomy are to be regarded as mutually comparable.

In making the nitrogen partitions the following substances were determined with methods as indicated: total nitrogen, Kjeldahl; urea nitrogen, Van Slyke and Cullen;[3] ammonia nitrogen, Van Slyke and Cullen;[3] creatinin, Folin and Morris;[4] creatin, Benedict;[5] purin nitrogen, Camerer-Arnstein.[6] In order to make the analytical data clearer, they are expressed in terms of the nitrogen content of the substances determined and in terms of the percentile amounts they represent of the total nitrogen excreted each day.

2. *Results.*—Adult dogs bear the effects of thyroidectomy remarkably well. Some of our animals lived comfortably for many months after the operation and without any obvious symptoms. This is to be explained by the fact that endocrine activity is probably lessened in the adult. Dr. F. M. Allen informs us that he has had similiar experience with thyroidectomized dogs at the Rockefeller Institute. Had it been practical to use young puppies for such difficult experiments, it is possible that the metabolic changes would have been more marked

1. Janney, N. W.: Jour. Biol. Chem., 1915, **20,** 321.
2. Janney, N. W., and Isaacson, V. I.: The Blood Sugar in Thyroid and Other Endocrine Diseases, THE ARCHIVES INT. MED., this issue.
3. Van Slyke, D. D., and Cullen, G. E.: Jour. Biol. Chem., 1914, **19,** 211.
4. Folin, O., and Morris, J. L.: Jour. Biol. Chem., 1914, **17,** 469.
5. Benedict, S. R.: Jour. Biol. Chem., 1914, **18,** 191.
6. Method of Camerer-Arnstein, "Analyse des Harns," Neubauer-Huppert, 1913, **2,** 941.

TABLE 1.—Dog 1. Nitrogen Partition

BEFORE THYROIDECTOMY

Day	Wt., Kg.	Glucose, Fed, Gm.	Vol. Urine, C.c.	Total N, Gm.	N per Kg.	Urea N		NH_3 N		Purin N		Creatin N		Creatinin N		Rest N	
						Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%
1	10.8	....	360	3.00	0.278	....	....										
2	10.6	....	370	2.58	0.243	....	....	....	..	0.013	0.50						
3	10.5	....	390	2.37	0.226	....	....	....	..	0.012	0.50						
4	10.4	....	400	2.33	0.226	....	....	....	..	0.011	0.48						
5	10.3	154.5	440	2.03	0.197	1.33	65	0.17	8	0.011	0.54	0.081	3.9	0.038	1.8	0.40	19
6	10.3	154.5	330	1.60	0.155	1.01	63	0.20	12	0.010	0.55	0.085	5.3	0.048	3.0	0.25	15
7	10.3	154.5	340	1.67	0.162	1.12	67	0.21	12	0.009	0.54	0.085	5.0	0.035	2.0	0.21	12
8	10.1	....	380	2.10	0.208	1.54	73	0.17	8	0.010	0.48	0.081	3.8	0.038	1.8	0.26	12
9	9.9	....	415	2.10	0.212	1.52	72	0.16	8	0.010	0.48	0.081	3.8	0.038	1.8	0.29	13

AFTER THYROIDECTOMY

1	12.2	....	600	1.65	0.136	1.16	70	0.16	9	0.006	0.36	0.101	6.1	0.015	0.9	0.21	13
2	11.8	....	540	1.96	0.166	1.39	73	0.17	8	0.003	0.15	0.100	5.4	0.014	0.7	0.30	12
3	11.7	175.5	210	1.91	0.163	1.23	64	0.18	9	0.004	0.22	0.110	5.7	0.021	1.1	0.36	20
4	11.7	175.5	200	1.65	0.141	1.07	65	0.21	12	0.006	0.36	0.119	7.2	0.020	1.2	0.23	14
5	11.7	175.5	260	1.69	0.145	0.99	60	0.22	13	0.008	0.48	0.126	7.4	0.014	0.8	0.37	18
6	11.7	....	430	2.07	0.177	1.58	76	0.14	7	0.006	0.29	0.106	5.1	0.035	1.7	0.20	10
7	11.5	....	440	2.07	0.180	1.61	77	0.13	6	0.004	0.19	0.106	5.1	0.035	1.7	0.21	10

TABLE 2.—Dog 2. Nitrogen Partition

BEFORE THYROIDECTOMY

Day	Wt., Kg.	Glucose, Fed, Gm.	Vol. Urine, C.c.	Total N, Gm.	N per Kg.	Urea N		NH_3 N		Purin N		Creatin N		Creatinin N		Rest N	
						Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%
1	17.6	....	535	3.03	0.172	2.27	74	0.21	7	0.021	0.69	0.21	6.9	0.026	0.85	0.29	9.5
2	17.3	....	575	3.11	0.180	2.44	78	0.23	7	0.012	0.38	0.22	7.0	0.038	1.22	0.17	5.4
3	16.6	249	450	3.12	0.188	1.83	58	0.30	9	0.030	0.96	0.23	7.3	0.016	0.51	0.71	22.7
4	16.6	249	345	2.47	0.148	1.71	69	0.24	9	0.026	0.75	0.18	7.2	0.038	1.13	0.28	11.3
5	16.6	249	510	2.55	0.154	1.79	70	0.24	9	0.020	0.79	0.18	7.0	0.038	1.46	0.28	10.9
6	16.5	....	770	3.14	0.190	2.54	80	0.21	8	0.020	0.65	0.20	6.3	0.022	0.70	0.30	4.7

AFTER THYROIDECTOMY

1	14.9	....	610	2.22	0.149	*	....	.....	..	0.015	0.69	0.18	8	.....	....	....	..
2	14.7	....	610	2.27	0.154	1.63	72	0.317	14	0.006	0.26	0.18	8	.....	....	....	..
3	14.5	217.5	610	2.58	0.177	1.96	76	0.188	7	0.022	0.84	0.18	7	0.022	0.86	0.21	9
4	14.5	217.5	505	1.78	0.122	1.06	60	0.366	20	0.020	1.10	0.17	9	0.004	0.25	0.16	8
5	14.5	217.5	570	1.65	0.113	1.08	66	0.206	12	0.015	0.89	0.17	10	0.023	1.39	0.16	9
6	14.5	....	430	2.19	0.151	1.72	77	0.145	7	0.013	0.58	0.17	8	0.023	1.05	0.11	7

* Urea N. + NH_3N = 1.85 gm. = 83 per cent. total N.

TABLE 3.—Dog 3. Nitrogen Partition

BEFORE THYROIDECTOMY

Day	Wt., Kg.	Glucose, Fed, Gm.	Vol. Urine, C.c.	Total N, Gm.	N per Kg.	Urea N		NH_3 N		Purin N		Creatin N		Creatinin N		Rest N	
						Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%
1	7.5	...	325	2.17	0.289	1.71	79.0	0.096	4.45	0.011	0.507	0.069	3.25	0.036	1.66	0.248	11.4
2	7.4	...	305	2.13	0.288	1.73	81.1	0.101	4.76	0.012	0.563	0.069	3.24	0.035	1.64	0.183	8.6
3	7.2	108	265	1.82	0.253	1.19	65.2	0.092	5.12	0.011	0.604	0.071	3.90	0.037	2.03	0.419	23.0
4	7.2	108	250	1.43	0.199	0.77	53.9	0.166	11.6	0.009	0.629	0.069	4.82	0.037	2.59	0.396	27.8
5	7.2	108	240	1.43	0.199	0.79	55.0	0.152	10.6	0.009	0.629	0.069	4.82	0.018	1.26	0.392	27.4
6	7.1	...	400	1.62	0.228	1.21	74.8	0.138	8.49	0.004	0.247	0.068	4.20	0.015	0.93	0.173	10.7
7	6.9	...	250	1.63	0.236	1.21	74.4	0.100	6.16	0.008	0.491	0.069	4.23	0.023	1.41	0.220	13.5
AFTER THYROIDECTOMY																	
1	7.0	.....	250	2.65	0.379	1.92	72.5	0.50	19.7	0.007	0.26	0.062	2.3	0.037	1.4	0.12	4.5
2	6.9	.....	290	2.72	0.395	1.99	73.1	0.46	16.9	0.007	0.24	0.055	2.8	0.043	1.6	9.16	5.9
3	6.8	.....	320	2.94	0.433	2.13	72.5	0.60	20.5	0.007	0.24	0.056	1.9	0.048	1.6	0.10	3.4
4	6.7	100.5	235	2.73	0.408												
5	6.7	100.5	225	2.07	0.309												
6	6.7	100.5	285	1.99	0.278												
7	6.55	.....	210	2.13	0.325												
8	6.55	.....	345	3.09	0.472												

TABLE 4.—Dog 4. Nitrogen Partition

BEFORE THYROIDECTOMY

Day	Wt., Kg.	Glucose, Fed, Gm.	Vol. Urine, C.c.	Total N, Gm.	N per Kg.	Urea N		NH_3 N		Purin N		Creatin N		Creatinin N		Rest N	
						Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%
1	6.3	....	235	1.95	0.309	1.62	83.0	0.079	4.07	0.008	0.41	0.060	3.0	0.026	1.3	0.157	8.0
2*	6.2	....	275	1.88	0.303												
3	6.0	....	235	1.60	0.267	1.32	82.5	0.053	3.28	0.006	0.37	0.060	3.7	0.026	1.6	0.135	8.4
4	5.9	....	230	1.65	0.280	1.38	83.8	0.051	3.06	0.007	0.42	0.060	3.6	0.030	1.8	0.121	7.4
5	5.8	87.0	220	1.35	0.233	0.90	66.3	0.090	6.66	0.010	0.74	0.057	4.2	0.035	2.5	0.262	19.2
6	5.7	85.5	115	1.16	0.203	0.75	64.6	0.078	6.71	0.006	0.51	0.060	5.1	0.044	3.7	0.222	19.1
7	5.7	85.5	205	1.28	0.224	0.82	64.0	0.090	7.03	0.008	0.67	0.060	4.7	0.036	2.8	0.266	20.4
8	5.6	....	225	1.23	0.220	†	....	.....	....	0.009	0.73	0.056	4.5	0.029	2.3	0.156	12.7
AFTER THYROIDECTOMY																	
1	5.30	....	105	1.85	0.349	1.52	82.1	0.089	4.8	0.005	0.28	0.061	3.06	0.038	1.9	0.14	7.6
2	5.25	....	210	1.71	0.326	1.33	77.8	0.087	5.0	0.005	0.30	0.053	3.10	0.036	2.0	0.20	11.7
3	5.10	....	185	1.51	0.300	1.25	82.7	0.080	5.3	0.005	0.33	0.056	3.71	0.020	1.3	0.10	6.6
4	5.00	....	155	1.60	0.320	1.33	83.1	0.086	5.3	0.005	0.31	0.057	3.56	0.019	1.2	0.10	6.2
5*	4.95	73.0	155														
6	5.00	73.0	105	0.98	0.196												
7	5.00	73.0	170	0.93	0.186												
8	5.00	....	200	0.98	0.196												
9	4.95	....	255	1.43	0.287												

* Specimen contaminated with feces.
† Urea N + NH_3N = 0.98 gm. = 80 per cent. total N.

This must be borne in mind in interpreting the results. It is also to be remembered that it requires a certain length of time for the myxedematous condition to develop after thyroidectomy. The metabolic disturbances reported by us, observed as they were at most a few weeks after the operation, are probably to be regarded as incipient.

Weight: Three of the four dogs had lost weight at the time of the examination and one had gained. The primary loss of weight may be caused by defective tissue nutrition due to the failure of thyroid function. Later, obesity tends to develop.

Nitrogen: The nitrogen excretion showed an inconstant variation. In two dogs it was diminished, in Dog 3 distinctly increased, while in Dog 4 no definite change took place. A decrease in the nitrogen elimination after thyroidectomy has been recorded by others.[7] Underhill and Hildilch[8] observed no very definite change.

Urea and Ammonia Excretion: The urea and ammonia varied in general with the total nitrogen excretion. In estimating changes in the metabolism, the experimental days on which glucose was fed are omitted from this discussion, as sugar disturbs the equilibrium of the nitrogen metabolites in the urine. The ammonia-nitrogen curve parallel's, as usual, the total nitrogen, except in the case of Dog 3, in which animal it was unusually increased after thyroidectomy.

Purins: Here the most striking changes were observed. In every instance the thyroidectomy was followed by a distinct diminution in the purins, as the average values in the accompanying tables demonstrate. These results appear to be the only ones recorded definitely indicating that the normal level of endogenous purin metabolism is maintained by the thyroid. The significance of this finding will be discussed later.

Creatinin: This remained practically uninfluenced by thyroidectomy except in Dog 1, in which it was somewhat increased. None of our work shows any definite influence of the thyroid on creatinin metabolism. The creatinin excretion showed its usual tendency to remain almost constant from day to day.

Creatin: This substance is usually present in dog urine, though abnormal in the urine of man. It showed fluctuations from zero in Dog. 2 after the operation to an increase after thyroidectomy in Dog 4. Creatin excretion is subject to wide variations, due to different causes, which have been discussed previously by Shaffer.[9] Such causes

7. Hunter, A.: Quart. Jour. Exper. Physiol., 1914, **8,** 21. Greenwald, I.: Biochem. Ztschr., 1913, **14,** 363.

8. Underhill, F. P., and Hildilch, W. W.: Am. Jour. Physiol., 1909-1910, **25,** 66.

9. Shaffer, P. A.: Am. Jour. Physiol., 1908, **23,** 1.

were evidently exerting their influence here. We were unable to detect any changes in the creatin metabolism definitely referable to thyroidectomy.

III. METABOLISM IN EXPERIMENTAL HYPERTHYROIDISM

1. *Experimental Plan.*—The effect of administering large amounts of thyroid substance on the urinary end-products of protein metabolism has been obscured in previous experiments through the introduction and consequent effect on the results of the protein, purin, etc., in the thyroid material ingested. To avoid this source of uncertainty we made use of a concentrated solution of the thyroid hormone isolated and kindly donated by Dr. E. C. Kendall of the Mayo Clinic. This was

TABLE 5.—HORMONE EXPERIMENT

Day	Wt., Kg.	Glucose Fed, Gm.	Vol. Urine, C.c.	Total N, Gm.	N per Kg.	Urea N		NH_3 N		Purin N		Creatinin N		Creatin N		Rest N		Special	
						Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Hormone Injected, C.c.	Urinary Glucose, Gm.
1	14.5	...	550	3.39	0.234	2.61	77	0.33	10	0.0056	0.16	0.19	5.6	0.0	0.0	0.25	7.5		
2	14.8	...	720	3.28	0.222	2.57	78	0.26	8	0.0112	0.34	0.19	5.6	0.0	0.0	0.25	7.6		
3	14.4	...	610	3.36	0.233	2.79	83	0.20	6	0.0098	0.26	0.18	5.4	0.0	0.0	0.18	5.3		
4	14.1	...	820	4.75	0.337	4.18	88	0.25	6	0.0147	0.30	0.19	4.0	0.038	0.8	0.08	1.7	35	
5	13.5	...	510	5.52	0.409	4.54	82	0.30	5	0.0224	0.40	0.19	3.5	0.125	2.2	0.34	6.1	15	
6	13.2	198	330	4.82	0.365	4.04	83	0.29	6	0.0217	0.45	0.19	3.8	0.070	1.4	0.21	4.3	15	2.2
7	13.4	201	630	5.07	0.378	4.06	80	0.37	7	0.0310	0.61	0.19	3.8	0.166	3.2	0.25	4.9	15	Trace
8	13.0	...	850	7.26	0.558	5.70	78	0.71	10	0.0430	0.59	0.19	2.5	0.085	1.1	0.54	7.4		
9	12.6	...	520	6.28	0.498	4.63	73	0.85	13	0.0220	0.35	0.15	2.3	0.066	1.0	0.56	8.8		
10	12.3	...	440	6.31	0.513	....	..	....	..										

analyzed by us. The doses administered contained so little nitrogen that the results cannot be influenced as mentioned. That this hormone preparation was active is not to be doubted, for it exerted a therapeutic effect on a cretin, as will be reported later in an experimental study of thyroid therapy.

The scheme adopted was to determine the normal fasting metabolism of nitrogen, urea, ammonia, etc., of a dog, after which large doses of the sterile hormone were injected subcutaneously. The methods employed have been alluded to in Section 2. The first hormone injection consisted of 35 c.c., which amount was reduced thereafter, 15 c.c. of the hormone being given daily. One c.c. of this liquid contained 0.96 mg. iodin, equivalent to about 3 mg. hormone. No local necrosis or infection followed the hormone injections. The

metabolic procedure was otherwise exactly that employed in the thyroidectomy experiments, fasting being maintained throughout.

2. *Results.*—This experiment afforded highly instructive results. A relatively enormous amount of the thyroid hormone was suddenly thrown into the organism. There ensued a latent period lasting until the following day. This phenomenon has been observed by Kendall. Then the temperature rose. The dog's skin became reddened. Hyperexcitability to touch developed, muscle twitchings following the slightest stimulus, increased reflexes and a distinct fine tremor of the paws were present. No exophthalmos was observed. It may be remarked that exophthalmos is very rarely seen in such experiments. Thus, Lampe, Liesegang and Klose[10] in their exhaustive monograph on exophthalmic goiter and experimental hyperthyroidism, report that they were able experimentally to produce protruding eyeballs only in certain degenerative strains of fox terriers. The clinical appearance of our animal was, with the exception noted, that of typical hyperthyroidism. After the hormone injections were discontinued, the symptoms gradually subsided.

Metabolism: Before the injections were given the excretion of the urinary nitrogenous substances was quite normal and regular, but thereafter a veritable metabolic storm broke loose. The total nitrogen practically doubled in amount during the next few days and remained high even after the hormone administration had ceased. The amounts of urea, ammonia and purins became correspondingly elevated. It is a remarkable fact that the creatinin remained absolutely unresponsive to this tremendous stimulus, and maintained its unchanged level throughout the experiment. Creatin, although absent previous to the injection, appeared in the urine in considerable amounts. The significance of this phenomenon is probably as follows: the hormone evidently caused a large increase of tissue and muscular breakdown of which creatin excretion is an evidence, providing, as in this case, it has been previously absent from the urine. The purin excretion of hyperthyroidism is especially interesting in view of the fact that the thyroidectomy experiments demonstrated that the purin metabolism is at least partly controlled by the thyroid. The purin elimination enormously increased during the period of hyperthyroidism; indeed, to the extent of 300 per cent.

Previous observations on the effect on the urinary nitrogen metabolites following the administration of thyroid material are but fragmentary. Cramer and Krause[11] observed what must of course take

10. Lampe, E., Liesegang, R. E., and Klose, H.: Beitr. z. klin. Chir., 1912, **77**, 757.

11. Cramer, W., and Krause, R. A.: Physiol. Soc. Proc., 1912, **23**, Jour. Physiol., 1912, **44**, 2.

place, that when the total nitrogen is increased by feeding thyroid material, a corresponding rise in the urea elimination ensues. Creatin appeared in the urine of their patient.

The Protein Sparing Action of Carbohydrates in Athyroidism and Hyperthyroidism. — In the foregoing experiments opportunity was afforded for testing an interesting hypothesis of special scientific interest. A recent research by us[2] has emphasized the important influence exerted by the thyroid gland on carbohydrate metabolism. Carbohydrates when taken into the body are known to limit protein breakdown. This process is most plausibly explained by the hypothesis that they thus "spare" protein by affording materials which are built up into protein, perhaps thus limiting tissue loss. The thyroid is now recognized as having a decided influence on the growth and nutrition of the tissues. If we then estimate the degree of protein-sparing by carbohydrate before and after thyroidectomy, we can determine whether this process is a function of the thyroid, consequently whether the thyroid possibly builds up the tissues by means of metabolic products of carbohydrates. The results of these experiments are quite negative. Glucose, as the protocols clearly show, spared usually as much protein before as after thyroidectomy. This action is therefore not controlled by the thyroid gland so far as is indicated by these experiments. This result has no special clinical significance. It only shows that in cretinism and myxedema the normal relationship of carbohydrate to protein metabolism is maintained.

Carbohydrate was also administered in the hyperthyroidism experiment. This was done in order to determine the effect of carbohydrate on the abnormally increased nitrogen metabolism observed in this condition. The protocol of this experiment shows no definite decrease in the total nitrogen and urea, and a decided increase in the purin excretion on the sugar days. During the following days all these substances were markedly increased. In interpreting these results one must bear in mind that during the injection days there was a tendency for a greater excretion of all the urinary substances examined, a result of the increasing toxic effect of the hormone. That this is true is demonstrated by a study of the purin elimination, which was largely increased even on the sugar days. Former investigation has shown that the effect of sugar on the protein metabolism is limited to urea and ammonia. The purins remained unaffected by the ingested glucose and were consequently relatively augmented in percentage. The ammonia in our case was not depressed by the sugar ingested. In view of this evidence of increasing tissue breakdown, the failure of the total nitrogen and urea to be decreased by the sugar administration, is not surprising, for without it the nitrogen and urea would likely have been excreted in increased amounts. The experiment is then

rather to be accepted as indicating that glucose exerts its sparing effect on protein metabolism also in hyperthyroidism. This experiment would thus offer an explanation for the results obtained by us in other experiments, to be reported later, showing that exophthalmic goiter patients do best on a mixed diet containing large amounts of nonnitrogenous foods, as the toxic loss of protein is partially combated in this way. The question of diet in thyroid diseases will be discussed in detail in a later communication.

IV. CLINICAL METABOLISM EXPERIMENTS

1. *Clinical Material.*—The cases included in the present study will be reported in detail in the third of this series of articles and are therefore but briefly extracted here.

Case 1.—Typical Cretin, Y. K., woman, aged 23; possessed the usual characteristics: short stature, pendulous abdomen, coarse skin, thickened nose and lips, defective teeth and nails; mental development, that of a child of 6 years. The patient, who remained in the metabolic ward for nearly a year, improved somewhat on thyroid treatment.

Case 2.—Exophthalmic goiter; A. H., man, aged 30; history of great loss of weight, increasing weakness and nervousness. The patient showed emaciation, constant fine tremor of hands, muscle twitchings, moist skin, large struma, with loud systolic bruit, marked exophthalmos; Stelwagen's and von Graefe's sign present. Prolonged metabolic studies demonstrated that his general metabolism was markedly increased, for it was necessary for him to consume 60 calories per kilogram to maintain weight equilibrium.

2. *Experimental Plan.*—Use was made of the advantages offered by a metabolism ward, special diet kitchen and nurses trained in metabolism work. The technic employed by us in metabolic examinations of patients has been previously described in various publications, and therefore scarcely requires a detailed presentation. The usual care was given to the weighing of the food and collection of the excreta. The patients had already undergone a careful training in the ward, where they had been for several months for other experimental purposes. The results may be therefore regarded as reliable. The diet was purin-free for one week prior to and during the examination, was weighed and consisted of the following articles: oatmeal, farina, rice, egg, corn, tomato, onions, bread, butter, crackers, milk, orange, prunes, pears.

Under these conditions nitrogen partitions as before were carried out on these patients with an idea of determining the influence of thyroid disease on the urinary nitrogen metabolites.

3. *Nitrogen Partition in Cretinism.*—The total nitrogen of the diet, as the protocols show, about equals the output, so that little nitrogen was lost or retained. The nitrogen elimination was low, but this seems due rather to the low protein, high carbohydrate and fat diet which necessarily constitutes a purin-free régime, than to any inherent ten-

dency of the cretin to a low nitrogen excretion. The urea, ammonia and creatinin showed normal variations. Creatin was present, which is abnormal. The purin nitrogen and phosphates ranged in the lower level of the normal excretion of these substances. The purins averaged 0.119 gm. daily. Normal variations are 0.08 to 0.25 gm. daily.

Scholz[12] has previously studied the urine of cretins in an extensive research published in 1905 when, unfortunately, few of the analytic methods were very reliable. This fact, together with the uncertain

TABLE 6.—Y. K.; CRETIN. URINARY NITROGEN PARTITION

Date	Vol. Urine, C.c.	N Intake, Gm.	Total N Gm.	Urea N		NH_3 N		Purin N		Creatinin N		Creatin N		Rest N		P_2O_5, Gm.
				Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
9/5	685	10.40	7.01	5.84	83.3	0.33	4.7	0.119	1.69	0.260	3.7	0.028	0.40	0.43	6.1	1.33
9/6	1,470	10.42	7.11	5.95	83.7	0.44	6.1	0.126	1.77	0.292	4.1	0.008	0.42	0.30	4.2	1.49
9/7	1,154	10.42	6.81	5.47	80.3	0.50	7.4	0.118	1.71	0.299	4.4	0.033	0.48	0.47	6.8	1.13
9/8	870	10.40	6.78	5.56	81.1	0.49	7.6	0.113	1.73	0.268	3.9	0.008	0.12	0.34	5.0	1.52
10/31	820	8.00	6.14	...	...	...	...	.....	....	0.319	5.2	0.023	0.37	....	...	....
11/1	800	8.04	7.04	...	...	...	...	.....	....	0.319	4.5	0.023	0.33	....	...	....
11/6	998	8.11	5.51	...	...	...	...	.....	....	0.318	5.8	0.024	0.44	....	...	....

TABLE 7.—J. H. EXOPHTHALMIC GOITER. URINARY NITROGEN PARTITION

Date	Vol. Urine, C.c.	N Intake, Gm.	Total N Gm.	Urea N		NH_3 N		Purin N		Creatinin N		Creatin N		Rest N		P_2O_5, Gm.
				Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
9/5	1,320	14.94	9.84	7.40	75.0	0.85	8.6	0.191	1.9	0.354	3.6	0.041	0.41	1.01	10.0	2.25
9/6	1,175	14.98	9.92	7.46	75.2	0.78	7.9	0.187	1.9	0.343	3.5	0.024	0.24	1.13	11.4	2.54
9/7	1,245	14.94	9.80	7.35	74.1	0.90	8.3	0.162	1.6	0.352	3.6	0.0	0.0	1.04	10.6	2.35
10/31	1,300	11.68	7.96	....	....	....	...	0.123	1.5	0.362	4.5	0.023	0.30	....	....	.....
11/1	1,500	11.50	7.99	....	....	....	...	0.086	1.1	0.323	4.0	0.023	0.29	....	....	.....
11/6	1,410	11.85	9.76	....	....	....	...	0.040	0.5	0.328	3.4	0.047	0.48	....	....	.....

activity of the thyroid preparations used at the time, would adequately account for the considerable variations shown by his results. His work, however, indicated that in the cretin, uric acid and phosphates and creatinin, the last in variance with our results, were eliminated in decreased amounts. McCrudden[13] found creatin present in the urine of a cretin, also in cases of infantilism and achondroplasia. Greenwald[14] confirmed certain of these results.

12. Scholz, W.: Ztschr. f. exper. Path. u. Therap., 1905-1906, **2**, 271.
13. McCrudden, F. H.: Jour. Exper. Med., 1912, **15**, 467.
14. Greenwald, I.: THE ARCHIVES INT. MED., 1914, **14**, 374.

4. *Nitrogen Partition in Exophthalmic Goiter.*—In these experiments the total nitrogen in the urine was found to about equal the intake. Protein metabolism in this case was undoubtedly increased, as a long series of later observations not appearing in this article, amply demonstrated. The urea nitrogen was normal in percentile relation to the total nitrogen. The ammonia tended to be high. In three of the four partition days, creatin was present in the urine. That creatin was consistently excreted in this case is shown by subsequent examinations as follows: Oct. 31, 1916, creatin 0.023 gm.; Nov. 1, 1916, creatin 0.023 gm.; Nov. 6, 1916, creatin 0.047 gm. The purin nitrogen and phosphate excretion were at the upper level of normal. In view of the striking increase of purin metabolism found by us in experimental hyperthyroidism, it is more likely that the purins will, on examination of a series of cases of uncomplicated hyperthyroidism, be likewise found increased rather than decreased, as reported by Falta and Zehner.[15] The creatinin in our case was a little low. Forschbach[16] has reported the same observation. As creatinin remains unaffected in experimental hyperthyroidism (see the foregoing), it is probable that its increase here is to be explained by the fact that sometimes the appearance of creatin is accompanied by a diminution of the amount of creatinin eliminated, the creatin being apparently formed at the expense of the creatinin. Excretion of creatin in exophthalmic goiter has been studied by Shaffer[9] and has been observed by others.

V. DISCUSSION AND CONCLUSIONS

We may now endeavor to piece together the results of the nitrogen partitions in the various experiments described, and draw from them what general conclusions are justified with regard to the urinary nitrogenous substances in our studies. No selective action of the thyroid was observed on urea and ammonia. The percentages of these substances remained within normal limits. The amounts present varied with the total nitrogen, in the usual manner. Our experimental studies definitely demonstrate that the thyroid exerts an influence on purin metabolism, as we observed both a decrease in the urinary purins after thyroidectomy and a marked increase in experimental hyperthyroidism; also a tendency to a low purin excretion in the cretin and a high excretion in a case of exophthalmic goiter. The clinical observations thus tend to confirm the experimental findings but should be extended before conclusions are justified.

The behavior of the purin metabolism in hypophysial disease seems to be analogous to that in thyroid disease. In the few cases investi-

15. Falta, W.: Die Erkrankungen der Blutdrusen, Berlin, 1913, p. 66.
16. Forschbach: Arch. f. exper. Path. u. Pharmakol., 1907, **63**, 113.

gated, the endogenous purin excretion is reported high in acromegaly by Falta and Nowaczynski.[17] The same investigators found a decreased uric acid elimination in hypopituitarism (Fröhlich's syndrome). The observation that the thyroid exerts an influence over purin metabolism analogous to the effect of the hypophysis is important, and a further illustration of the fact which is becoming more and more apparent, namely, that several of the endocrine organs may exert very similar influences on the metabolic processes.

With regard to clinical applications, it might seem, in view of these results, justifiable to seek the cause of gout in an endocrine disturbance. So far, however, as the thyroid and hypophysis are concerned, clinical observations do not support a relation of diseases of these organs to gout. One might likewise feel inclined to administer thyroid or pituitary tablets to gouty patients in the hope of stimulating the excretion of the purins. According to our views, however, this would scarcely be advisable, at least in the case of thyroid, for it is probable that the excretion of purins is increased only as the result of a toxic effect of large doses of thyroid on the protein of the tissues (compare hormone experiment).

Our studies emphasize the independence of the creatinin metabolism from thyroid influence. Creatinin was not increased in the urine even when large amounts of body tissue were being broken down in experimental hyperthyroidism. This would seem to indicate that creatinin is not a direct product of protein catabolism. With regard to creatin, it is indeed strange that a product which is chemically merely hydrated creatinin should appear in the urine while the creatinin undergoes but little change. This apparent independence of creatin from creatinin metabolism is striking. A number of previous observations have, however, shown this to occur under other circumstances.

In the thyroidectomy experiments the creatin determinations are not very valuable, as this substance is usually present in normal dog urine. However, the fact that it is found in cretinism and exophthalmic goiter deserves consideration. Creatin is usually excreted when masses of body tissue are being broken down, such as takes place in severe febrile conditions. Such is, however, not the case in cretinism. Its appearance in this condition is probably due to a disturbance in the normal synthetic metabolic processes which take place by means of intermediary chemical reactions which are as yet little understood, but may be disturbances in the metabolism of carbohydrates. The creatinuria of exophthalmic goiter seems more easy of comprehension than that of cretinism, for in exophthalmic goiter there is frequently a toxic breakdown of body tissue which may be held to account for the appearance of creatin.

17. Falta, W.: Ductless Glandular Diseases, Philadelphia, 1916, p. 263.

The present experiments do not support the view that any marked diminution of nitrogen excretion follows thyroidectomy in animals (see the foregoing). Nor was the nitrogen output particularly low in the cretin. There are, moreover, reasons to believe that the decrease in the protein breakdown, observed by others in the cretin metabolism, is due rather to an inability for growth and repair of tissue to take place. These views will be more fully developed in the next article of this series.

We wish to acknowledge the excellent assistance rendered by Miss Maude Hays in the dietetic and analytic work of this research.

III. STUDIES IN THYROID THERAPY

THE EFFECTS OF THE THYROID HORMONE AS DETERMINED BY A CLINICAL METABOLIC AND DIETETIC INVESTIGATION. NEW POINTS OF VIEW ON THYROID FUNCTION IN HEALTH AND DISEASE *

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I. INTRODUCTION AND SUMMARY

Of all attempts at organotherapy, the most brilliant results have been obtained with thyroid preparations. This fact lends especial interest to the isolation of the active substance of the thyroid, as well as its employment in the treatment of disease. Some time ago a crystalline body containing upwards of 60 per cent. of iodin was prepared from the thyroid by Kendall of the Mayo Clinic. Observations made on cretins and myxedema patients justify the view that this substance is to be regarded as a hormone having the functions ascribed to the thyroid. Some time back Dr. Kendall generously presented me with a quantity of this material for independent study.

The present article describes therapeutic experiments with this thyroid preparation, the effect of thyroid administration on metabolism, and of diet in thyroid disease. In view of the importance of a thorough study of the thyroid hormone, it was decided to follow its action with the aid of (1) concomitant metabolic investigations, (2) strict control of the dietary régime by specially analyzed and weighed diets, (3) prolonged periods of observation (varying from three to thirty-seven weeks), (4) parallel observations of the effect of other thyroid preparations, (5) series of normal control cases.

On account of the unusual amount of special food preparation, special nursing, and analytic work required, only a limited number of cases could be included. All deductions made in this article are therefore subject to this criticism. It is, however, believed that less material thoroughly studied is of greater value than a larger number of cases which have been merely subjected to the usual clinical methods of control.

In order to establish a definite gage of the activity of the thyroid preparations given it was determined to follow the effects on the pro-

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* From the Montefiore Hospital, New York City. A preliminary report of this research was read before the Academy of Medicine, Section of Internal Medicine, New York, December, 1916.

tein metabolism over continued periods, with estimation of the nitrogen intake, output and balance. It was found that the nitrogen balance is a rather delicate measure of the action of the hormone. *The results are of unusual interest, for they very definitely indicate that a gain, not a loss, of nitrogen is a result of the therapeutic action of the thyroid; and vice versa, that a loss of nitrogen, that is, protein, is due to a toxic action of the gland.*

The thyroid hormone was found to have a definite therapeutic effect in cretinism, improvement in the clinical symptoms and a gain in nitrogen retention resulting. The optimal daily dose was found to be 0.25 mg. hormone iodin, representing approximately 0.75 mg. hormone, and corresponding to 4 grains of thyroid tablets. It could thus be demonstrated that usually too great an amount of thyroid is prescribed in hypothyroidism. The use of the thyroid hormone in minimal doses, that is, 0.02 to 0.06 mg. hormone iodin daily in Graves' disease, was followed by increased retention of nitrogen but by no certainly established therapeutic effect. The thyroid treatment of obesity depends on a toxic effect, as it is accompanied by nitrogen loss. It should therefore be discouraged.

The effect of diet in thyroid disease was also critically reviewed and investigated. In cretinism, as in normal individuals, an evenly balanced protein, fat and carbohydrate diet is followed by the best results. In exophthalmic goiter, as has been previously observed, very greatly increased amounts of food are necessary in order to combat the toxic combustion. A high caloric mixed diet was found to be the diet of choice in this condition. The relation of diet to the therapeutic action of thyroid preparations was also investigated.

From this and other studies[1] of the thyroid problem, certain changes in point of view toward thyroid function in thyroid diseases are developed and included in the general discussion. They comprise (1) the conception of the anabolic and therapeutic action in contradistinction to the catabolic or toxic action of the gland or its preparations; (2) a discusion of metabolism in hypothyroidism; (3) the hormone hypothesis of the pathogenesis of exophthalmic goiter.

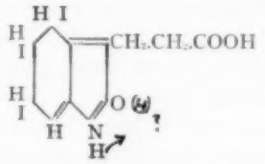
II. THE PREPARATION AND PROPERTIES OF THE THYROID HORMONE

For the isolation of the thyroid hormone the profession is indebted to Dr. E. C. Kendall.[2] The principles of its separation are hydrolysis of thyroids by sodium hydroxid into *a*-iodin proteins, insoluble in

1. Janney, N. W., and Isaacson, V. I.: The Effect of Thyroidectomy and Thyroid Diseases on the Protein Metabolites, and The Blood Sugar in Thyroid and Other Endocrine Diseases, in this issue.

2. Kendall, E. C.: Fed. Am. Soc. Exper. Biol., New York, Dec. 30, 1916; Collected Papers, Mayo Clinic, 1916; Jour. Biol. Chem., 1915, **20**, 501.

acids, and *b*-iodin proteins soluble in acids. In the *a*-iodin fraction is contained 2 to 50 per cent. of the total iodin in the gland. This fraction alone seems physiologically active. From it was later isolated a body crystallizing in microscopic sheaths containing 65 per cent. iodin, of the high atomic weight 586, having the formula $C_{11}H_{10}O_3NI_3$, being structurally according to Kendall tentatively as follows:



Here it may be said that this compound still awaits satisfactory identification by publication of the detailed methods of isolation, elemental analyses, and complete proof of the correctness of the structural formula by synthesis or otherwise, and finally confirmation of these results. Before this crystalline substance can be accepted as the thyroid hormone, however, the main question to be answered is its physiologic activity. This point has been answered by work done at the Mayo Clinic, which showed not only that toxic symptoms produced by the thyroid gland or its extracts are also produced by this isolated substance, but also that it causes cretins to grow and return to their normal condition. The present article goes far toward confirming these results. Apparently but one hormone is present in the thyroid.

A considerable difference in the action of the hormone on dog and man was found by Kendall to exist. In the canine 1 mg. per kilogram body weight is required for toxicity while $\frac{1}{75}$ to $\frac{1}{25}$ of 1 mg. per kilogram body weight per day has caused toxic symptoms in man. The toxic period is preceded by a latent period of one or more days and includes increased pulse rate, irritability to touch, fine tremor, increased appetite, then nausea and diarrhea.

The production of the thyroid hormone has not as yet attained commercial proportions. The largest amount as yet obtained is 20 gm.[3]

III. EXPERIMENTAL TECHNIC

The general methods employed here have been previously alluded to in various articles by the author and his co-workers.[1] The effects of extraneous influences on the patients were avoided by having them occupy separate rooms in a metabolic ward one or two weeks previous to and during the examination, and by permitting no other treatment in addition to thyroid therapy except prescribed periods of rest, fresh air and walking. Special nurses trained in this work were employed

3. Kendall, E. C.: Verbal communication.

and the patients remained under constant control day and night. Previous to the experimental periods, each patient was put through a preliminary training in keeping faithfully to the prescribed weighed diet, and in accurate collection of urine and feces. With the help of properly trained nurses, we have found no difficulty in collecting an exact twenty-four-hour specimen of urine from even female patients over long periods of time. The regularity of the values recorded in the protocols is the best proof which can be afforded of this statement. The cases here reported were selected from among patients taken into the ward but not found adaptable to exact study.

The dietaries employed were calculated on the basis of Meeh's weight-height formula for the basal requirement, allowance being made for sex, age, activity and the elevation or depression of the total metabolism in thyroid conditions. Practically every article of food was sampled and analyzed for nitrogen, and the articles in the diet selected as simply as possible to avoid all possible errors in this regard. In spite of this, experience has shown that it is very difficult to attain absolute exactness. It must be remembered, however, that it is the relative differences rather than the absolute values that are of importance in these metabolic experiments. It seems superfluous to enumerate the various constituents of the dietaries.

The Nitrogen Balance. — In obtaining this value, the various amounts of nitrogen in the separate foods were calculated, and the total nitrogenous intake of the day balanced against the sum of the nitrogen excreted in the urine and feces. The twenty-four-hour urine was regularly collected. For greater accuracy, the feces were segregated usually at weekly intervals, the weekly amount dried, and the nitrogen estimated. Although regularly made, slight importance was attached to the daily balances. On account of the large number of daily balances (500 to 600) the daily protocols reproduced in this article are limited to a few specimen periods. Generally weekly periods are represented giving the average value of the nitrogen of the food, urine, feces and balance figures.

The hormone was preserved in sterile neutral solution. It was conveniently administered in the form of weak standard solutions, 1 c.c. containing 0.01 or 0.001 mg. iodin. The hormone preparation sent us by Dr. Kendall contained 32 per cent. iodin, so that the actual amount of hormone given was about three times that of the iodin. Although our preparation contained other substances than the hormone, which accounts for its lower iodin content, they proved to be physiologically inactive, both in the experience of Dr. Kendall and ourselves, and do not, therefore, influence the results. We have used the iodin content of the hormone as a

standard for dosage throughout the present paper and refer, therefore, to the hormone iodin or H. I., rather than to the hormone itself.

We have found it convenient to administer the hormone by mouth. In the form in which it is employed by us, it is tasteless. Its therapeutic action is not affected by its passage through the gastro-intestinal tract. For this statement we have the evidence of accumulated clinical experience, as the oral method of thyroid medication has been used with good results.

As previously noted by Kendall, our hormone preparation though remaining active over many months, eventually suffered deterioration. This suggests that even excellently prepared thyroid tablets, whose effect depends on the hormone contained in them, should be expected to lose their effect in time. This fact is confirmed by clinical experience.

IV. CONTROL EXPERIMENTS

As therapeutic effects are obtained by small doses of thyroid, it was decided to endeavor to detect metabolic and other changes by this means, rather than to follow the action of markedly toxic doses as had already been frequently done by other investigators. Endocrine activity is greater in the young; therefore two of the selected three cases were children.

CASE 1.—S. M., girl, aged 12 years. Diagnosis, fully compensated endocarditis. This patient's requirement was 1,887 calories, but throughout the experiments diets supplying approximately 2,100 calories were given. The purpose of this increase was to exclude the effects of an overrestricted diet on the nitrogen balance, it being known that under these circumstances nitrogen may be lost due to tissue combustion for fuel purposes. That an adequate diet was given is shown by the gain in weight, which amounted to 3 pounds and 4 ounces during the two months of the experiment.

TABLE 1.—S. M. CONTROL CASE

Period	Date	Change in Weight, lb. oz.	N Intake, Gm.	N in Urine, Gm.	N in Feces, Gm.	N Balance, Gm.	Medication	Diet			
								Prot., Gm.	Fat, Gm.	Carb., Gm.	Cal.
1	7/ 6-11*	— 2	3.23	2.33	1.16	—0.21	None	20	58	268 (7/6-19)	2,130
2	7/13-19†	— 4	3.28	1.98	1.37	—0.07	0.38 gm. gland				
3	7/23-29	+1 2	12.04	9.15	0.95	+1.93	None	77	87	245 (7/20-8/8)	2,111
4	7/30-8/5	+ 12	11.94	8.57	0.85	+2.62	None				
5	8/ 6-12	+ 4	12.04	8.85	0.92	+2.28	0.38 gm. gland				
6	8/13-19	+ 2	11.92	9.33	1.10	+1.49	0.38 gm. gland				
7	8/20-26	+ 10	12.15	9.19	1.56	+1.41	0.005 mg. H. I.				
8	8/27-9/8	+ 12	12.19	8.81	0.85	+2.52	None				

* July 12, balance omitted. Diet unchanged.
† July 20-23, balance omitted to allow change of diet to have its effect.

During Periods 1 and 2, a diet very low in nitrogen was given. After having been a week on the diet, on which the patient lost weight and showed a negative nitrogen balance, it was decided to determine the effect of a minute dose of thyroid (0.38 gm. gland). Practically no clinical or metabolic changes took place.

The diet was then altered to a normally mixed diet. After having observed a two weeks' balance without medication, the same amount of fresh gland was again administered. During Periods 5 and 6, a depression of the nitrogen balance as compared to that of the foreperiods was noted, also a tendency for less weight to be gained. In Period 7, during which 0.005 mg. hormone iodin was prescribed, the nitrogen balance remained low, although a tendency to gain weight was resumed. After stopping the medication in Period 8, a higher plus balance and increased weight resulted. It will be noted that during the medication Periods 2, 6 and 7, increased amounts of nitrogen were lost in the stools, which loss ceased when the thyroid ingestion was stopped. The clinical condition remained unchanged throughout.

CASE 2.—A. S., girl, aged 12 years. Diagnosis, chronic endocarditis, fully compensated. This patient's requirement was 1,738 calories. She remained on a normal mixed diet supplying 2,088 calories during the entire period of examination.

TABLE 2.—A. S. CONTROL CASE

Period	Date	Change in Weight, lb. oz.	N Intake, Gm.	N in Urine, Gm.	N in Feces, Gm.	N Balance, Gm.	Medication	Diet			
								Prot., Gm.	Fat, Gm.	Carb., Gm.	Cal.
1	4/10-17	+1 12	10.53	7.08	1.05	+2.40	None	62	56	197	2,088
2	4/18-24	— 2	10.52	7.22	1.13	+2.17	0.32 gm. gland	(Diet throughout)			
3	4/25-5/1	+ 12	10.54	7.38	1.17	+1.99	0.32 gm. gland†				
4	5/ 2- 8*	+1 4	10.54	7.70	1.23	+1.60	0.16 gm. gland‡				
5	5/16-22	+ 12	10.54	8.15	1.47	+0.91	34 mg. tablet§				
6	5/23-26	+ 10	10.54	8.06	1.46	+1.02	17 mg. tablet				
7	5/27-29			7.54	1.29	+1.71	None				
8	5/30-6/5	+ 8	10.54	7.89	1.20	+1.43	8.5 mg. tablet				

* May 9-15 omitted. Diet unchanged. Error in collection.
† Medication stopped last two days.
‡ On last day, 34 mg. tablet given.
§ On May 19, changed to 17 mg. tablet.

An inspection of the protocols confirms the results obtained in the previous experiment. The same amount of fresh thyroid per kilogram of bodyweight as was given S. M. caused an increase in the urinary as well as the fecal nitrogen output and a consequent decrease in the balance. In Period 3 slight tachycardia developed, the thyroid was therefore discontinued for two days. One half the preceding dose was then administered. No clinical toxic symptoms were now observable but the nitrogen balance continued to decline. In Periods 5 and 6, Armour's thyroid tablets containing 0.2 per cent. iodin were given. The result was a further decrease in the nitrogen balance. When the thyroid medication was stopped for two days (Period 7) an increase in the balance occurred. The loss in the balance was resumed on the administration of 8.5 mg. tablet in Period 8. Aside from the toxicity exhibited in Period 3, the child's condition remained excellent throughout.

CASE 3.—B. C., woman, aged 25 years. Diagnosis, mild neurasthenia. Requirement, 1,645 calories. The diet supplied 1,545 calories and a sufficiency

of protein. The patient lost weight, which may have been due to the fact that her actual requirement was greater than the one calculated, due to greater muscular activity induced by her nervousness. Although there is no definite relationship between the loss of weight, in the case of this patient, and the thyroid administered, there is observable a distinct effect of the medication on the nitrogen balance. In Periods 2 and 3 when hormone iodin in doses of 0.01 and 0.02 mg., respectively, were given, it is seen that a very markedly depressant effect on the nitrogen balance ensued; the lowest balance being obtained when most hormone was ingested. In Period 4 when treatment was stopped, a tendency to a return to a higher balance was exhibited. The patient's clinical condition remained unchanged during the entire course of the experiment.

Conclusions from the Control Experiments.—The results of this series indicate that the normal organism is more sensitive to minute doses of thyroid than had been previously supposed. The earliest observable effect is a tendency for a positive nitrogen balance to diminish, this condition being sometimes accompanied by a loss of weight. The same effects were observed both on diets containing normal and decreased amounts of nitrogen, in the latter case the results being naturally less marked.

TABLE 3.—B. C. CONTROL CASE

Period	Date	Change in Weight, lb. oz.	N Intake, Gm.	N in Urine, Gm.	N in Feces, Gm.	N Balance, Gm.	Medication	Diet			
								Prot., Gm.	Fat, Gm.	Carb., Gm.	Cal.
1	9/16-22	—1 2	8.53	6.71	0.41	+1.42	0	53	65	197	1,545
2	9/23-29	+ 2	8.53	7.35	0.57	+0.61	0.01 mg. H. I.	(Diet throughout)			
3	9/30-10/6	— 14	8.56	7.36	1.04	+0.16	0.02 mg. H. I.				
4	10/7-13	—1 8	8.57	6.94	1.04	+0.59	0				

A decreased retention of nitrogen was obtained with fresh gland, Armour's tablets, and Kendall's hormone, when given to individuals with normally functioning thyroids. The deduction may therefore be drawn that the hormone is the active principle of the thyroid gland as it produces results identical with those obtained with the other preparations. Kendall's statements with regard to the specific action of the thyroid hormone receives, therefore, new corroboration.

Since a decreased nitrogen retention is observable in normal cases when thyroid preparations are administered, the inference may be drawn that in the case of normally functioning thyroids, the smallest amounts of hormone added from without tend to cause nitrogen loss. Reasons for regarding this effect as a toxic indication will be given later in the article. Identical doses of the hormone have a very different action in thyroid diseases as the following sections demonstrate.

V. CRETIN EXPERIMENTS

CASE 4.—*Abstract of Case History.*—Y. K., woman, aged 25 years; Austrian Jewess. Diagnosis, sporadic cretinism. From birth, growth and intelligence were markedly subnormal. The large head and abdomen receded somewhat in size on beginning menstruating at the thirteenth year; dysmenorrhea and irregularity since; patient unable to learn at school; is both irritable and stupid.

Examinaton.—Typical cretin. Height, 4 feet 5½ inches; short, thick-set trunk, short extremities; intelligence that of child of 4 years; skin coarse and covered with coarse hair; speech guttural; vision defective; bulging forehead, saddle nose; teeth poorly calcified; tongue voluminous; large cystic goiter; right lobe larger; systolic bruit; circumference of neck, 15½ inches; heart not enlarged; functional murmurs at times; abdomen pendulous and fat; palms of hands and soles of feet padded; genitalia normal; pulse regular, 80 to 100 in rate; temperature 99 to 99.5; blood pressure normal; Wassermann test negative. Roentgen examination showed underdevelopment of anterior skull and face bones, absence of frontal sinuses, thickened occipital bones, thinned maxilla. Persistence of epiphyseal lines of long bones.

Experimental.—In the experiments on this patient not only the effect of administering various thyroid preparations in varying doses, but also the effect of diet was studied. The latter will be treated in a special section. During the first nine experimental periods the patent remained on a fixed weighed diet, containing the food classes in the usual relations and supplying 2,192 calories, or 50 calories per kilogram.

During Periods 2 and 3 the effect of the daily administration of 0.5 gm. fresh gland was studied. The patient, who had not received thyroid medication for a long time, became appreciably brighter mentally and ceased to complain of headache, with which she was constantly troubled when not treated with proper doses of thyroid. The effect on the nitrogen balance was striking, for though positive in the foreperiods, it increased by nearly 100 per cent. The weight also increased.

During Period 4, treatment was stopped. The balance remained high, however. This was probably due to the two weeks' previous treatment. In Periods 5 and 6 the fresh gland treatment was resumed. A decreased nitrogen balance was observed, which was, however, at a higher level than in Period 1. Clinically, the patient's condition improved steadily, her skin became clearer and her intelligence brighter.

The differences in the effect of the fresh gland is probably to be ascribed to the greatly varying iodin content of the thyroids of different animals. According to Seidell and Fenger[4] the iodin of the dried gland ranges from 0.04 to 0.33 per cent., undergoing seasonal and other variations. Differences in effect when identical doses were prescribed may be observed in the protocols. During Periods 7, 8 and 9, 50 mg. of thyroid tablets were prescribed. This dose was calculated to contain 0.05 mg. hormone iodin. That the amount was inadequate could be demonstrated from the fact that the cretin's headache returned, her clinical condition generally was not as good, and her metabolism was not as favorably influenced.

Low Protein Periods.—The cretin next went on a low protein, high carbohydrate diet, supplying about the same number of calories as previously. On this diet she evidently suffered from nitrogen deficiency and lost weight (Period 10). The administration of 0.5 gm. of fresh gland (Periods 11 and 12) did not benefit her markedly, although a tendency for a slightly increased balance was observable. From these periods the important deduction can be drawn that *a correct dietary is necessary to obtain a beneficial effect of thyroid treatment, also that the effect of the thyroid treatment is accomplished through its influence in increasing the power to assimilate a proper diet.* The results

4. Seidell, A., and Fenger, F.: Jour. Biol. Chem., 1912-1913, **13,** 517.

here obtained do not substantiate the generally quoted view that cretins require less nitrogen for maintenance than do normal individuals.

High Protein Periods.—During the next six periods (13 to 18, inclusive) the patient was given a high protein diet corresponding calorically very closely to the diets previously given. The initial gain in weight and nitrogen on this régimen (Period 13) was probably due to compensatory effects for the low protein of the preceding diet. In the next three periods (14, 15 and 16)

TABLE 4.—Y. K. CRETIN

Period	Date*	Change in Weight, lb.	oz.	N Intake, Gm.	N in Urine, Gm.	N in Feces, Gm.	N Balance, Gm.	Medication	Diet			
									Prot., Gm.	Fat, Gm.	Carb., Gm.	Cal.
1	2/13-19	−1	6	10.54	8.20	0.96	+1.39	0	67	96 (3/13-5/27)	242	2,192
2	3/28-4/3	+	6	10.54	7.06	1.05	+2.43	0.5 gm. gland				
3	4/4-10	+	4	10.54	6.95	0.97	+2.62	0.5 gm. gland				
4	4/16-22	+	6	10.54	7.15	1.05	+2.34	0				
5	4/23-29	+	10	10.54	7.19	1.23	+2.12	0.5 gm. gland				
6	4/30-5/6	+	12	10.54	7.25	1.61	+1.68	0.5 gm. gland				
7	5/7-13	±	0	10.54	7.35	1.11	+2.07	50 mg. tablet				
8	5/14-20	+	8	10.54	7.66	1.10	+1.78	50 mg. tablet				
9	5/21-27	+	2	10.54	8.13	1.12	+1.29	50 mg. tablet				
10	6/14-20	−	8	4.31	3.49	0.82	−0.01	0	27	99 (6/4-7/11)	229	1,906
11	6/28-4	±	0	4.31	2.91	0.72	+0.67	0.5 gm. gland				
12	7/5-11	−1		4.31	3.16	0.77	+0.38	0.5 gm. gland				
13	7/17-23	+1		16.06	9.65	2.21	+4.26	0	101	95 (7/12-8/25)	209	2,125
14	7/24-30	±	0	15.95	11.44	1.61	+2.89	0				
15	8/31-9/6	+	2	16.20	11.40	1.60	+3.02	0				
16	8/7-9	+	4	16.18	11.31	1.07	+3.80	0				
17	8/10-15	+	2	16.18	11.33	1.46	+3.36	0.48 mg. H. I.				
18	8/21-25	.....		15.26	11.98	1.74	+1.54	0.25 mg. H. I.				
19	9/5-11	+2		10.46	7.08	1.04	+2.35	0	As in Periods 1-9			
20	9/26-10/2	+	14	10.45	7.34	1.04	+2.07	0.5 gm. gland				
21	10/6-10	−2	14	7.96	7.57	0.64	+0.13	0	50	53	189	1,469
22	10/18-24	+	2	8.02	6.01	0.69	+1.32	0.25 mg. H. I.				
23	10/25-31	−	12	8.04	6.28	0.76	+1.00	0				

* Although the balance was omitted on the following dates the diet remained the same as in the preceding period: 3/20-27; 4/11-15; 6/21-28; 8/16-21; 9/25-10/2; 10/11-18.
On the following dates, 5/28-6/14; 7/12-17; 8/26-9/5; 10/3-6, the balance was omitted to allow the change of diet to have its effect.

less weight and nitrogen were gained. The patient, who had now gone without thyroid medication for a month, had experienced a return of her characteristic headaches. Her skin color and texture as well as her mentality, which had been improving under treatment, now failed to undergo further betterment.

After this comprehensive preliminary study, the first trial with the thyroid hormone was made. A daily dose of 0.48 mg. hormone iodin was given by mouth for six days (Period 17). This dose was evidently too large, for

mental excitability, tachycardia and precordial oppression soon developed. This toxic effect is reflected in the failure to gain nitrogen. An interval of four days, in which no thyroid was given, was not sufficient for the clinical toxicity to subside, for a reduction of the hormone dosage in Period 18 failed to influence favorably either the clinical symptoms or to prevent a further loss of nitrogen. The nitrogen balance for this period is consequently low. During the course of these investigations we have frequently noted that the toxic symptoms due to an overdose of thyroid may endure for some time after the medication has been stopped.

In spite of the pauses made in her treatment as well as the slight evidences of toxicity at times caused by overdosage, the cretin's general condition had considerably improved as compared to that of six months previously (Period 1). We therefore determined to have the patient return to her original diet in order to discover whether the clinical improvement was not reflected in her general metabolism. This was accordingly done (Periods 19 and 20). The results proved the correctness of our supposition. It was found that on the liberal mixed diet the patient gained 2 pounds in weight, though fat did not noticeably increase, and the nitrogen balance rose nearly to the height attained when most favorably influenced by the thyroid medication one-half a year before. In Period 20, with 0.5 gm. fresh gland, the nitrogen balance exhibited a tendency to fall rather than rise. For this result we have no satisfactory explanation, unless it be that temporarily no additional hormone was required, the dose here given acting in excess as in normal individuals.

The last series of experiments (Periods 21, 22 and 23) were planned to trace the effect of the hormone when the patient was on a bare maintenance mixed diet. During the preliminary period (21), the cretin lost 2 pounds and 14 ounces and the nitrogen balance approached zero. When 0.25 mg. hormone iodin was administered, weight ceased to be lost and the nitrogen balance jumped to plus 1.32 gm. daily, which is ten times that of the previous week. The clinical symptoms again confirmed these signs of improvement. When the hormone was stopped (Period 23) weight was again lost and the nitrogen balance tended to decrease. *These periods demonstrate in the most convincing fashion the therapeutic effect of the thyroid hormone.*

The effect of hormone treatment is well exemplified in the blood picture. On Aug. 17, 1916, the hemoglobin was 70 per cent., the erythrocytes 4,000,000; while on Nov. 17, 1916, the hemoglobin was 85 per cent., and the red count 4,800,000. The differential counts are likewise of interest, the lymphocytes decreasing during the same interval from 46 to 33 per cent. The mononuclear cells (4 to 12.5 per cent.) failed to show a corresponding decrease. Similar blood changes in myxedema and cretin cases undergoing treatment have been previously observed.

The weight changes in a cretin during a course of treatment are of interest. The resumption of growth is of course accompanied by a general increase of body weight. On the other hand, the amount of fatty tissue of the body usually decreases. There is thus exhibited a certain tendency to counterbalance gain with loss of weight, which must be taken into account. On beginning our observations, the patient's naked weight was 96 pounds (March 13, 1916), she reached a maximum weight of 106 pounds on Oct. 2, 1916, and declined to 99 pounds 4 ounces on Jan. 20, 1917, with the restricted diet used during this period. In our case, in spite of intermittent treatment, the increase of weight is thus seen to be quite large, amounting to 10 pounds, or 10 per cent. of the total. In view of the general improve-

ment, it can be considered as real growth, although the height was not affected, as was to be expected in view of the mature age of the patient.

Finally, the effect of treatment was also seen on the metabolism. Hypothyroid conditions are characterized by a delayed blood glucose curve in the sugar tolerance test.[5] Y. K. proved no exception. It is very striking, however, that the tolerance curve returned to normal after treatment. (See schema in article quoted.)

Conclusions from the Cretin Experiments.—The important fact brought out by this work is the effect of thyroid medication on cretin metabolism. The identical amounts of thyroid which caused nitrogen loss with or without toxicity in normal individuals led to a large gain in nitrogen accompanied with improvement in the clinical condition in the case of the cretin. This effect was so delicate that the nitrogen balance could be used as a gage of the correctness of the dosage. The therapeutic action of the thyroid is therefore anabolic and constructive, not catabolic and destructive. This point will be developed later in the discussion.

With regard to the practical application as to dosage, our observations were necessarily limited to a single patient. It is clearly shown, however, that 0.25 mg. hormone iodin daily is optional. Kendall has used with success doses varying from 0.125 to 0.333 mg. of hormone iodin in cretinism and myxedema, which our findings corroborate. It is important for the profession to recognize that the optimal tablet dosage is not large, as 0.25 mg. hormone iodin corresponds to about 4 grains thyroid tablets, on the basis that 50 per cent. of the iodin content is combined in the active substance. Four grains daily of the standard 0.2 per cent. iodin thyroid tablets may be regarded as a preferable trial dose. Hence the practice of prescribing large amounts of thyroid tablets, such as 5 grains three times a day to cretin and myxedema patients, can be expected to be followed by poor results. As, according to Kendall, the active *a*-iodin varies considerably in various glands, it is easy to understand how uncertain results may follow the use of tablets containing a standard amount of iodin. Thus, it is clear that the isolated hormone, when commercially obtainable, will supersede in reliability all present preparations.

VI. EXOPHTHALMIC GOITER EXPERIMENTS

In order to complete our observations, the effect of the thyroid hormone on exophthalmic goiter was studied. The same experimental plan was pursued as hitherto. In connection with varying dietetic régimes, the effect of the thyroid hormone on the nitrogen balance

5. Janney, N. W., and Isaacson, V. I.: The Blood Sugar in Thyroid and Other Endocrine Diseases, in this issue.

and clinical symptoms was observed. The action of various other thyroid preparations has been frequently studied in exophthalmic goiter; accordingly in our work only the effect of the hormone was investigated.

CASE 5.—M. F., man, aged 27, Hebrew, hospital orderly. Diagnosis, mild exophthalmic goiter. The family was neurotic but not goitrous. For the previous few months the patient had noticed a swelling of the neck and increasing nervousness. There was found the typical exophthalmic goiter psyche, slight exophthalmos and Stelwagen's sign, slight tremor of hands, increased perspiration, and a diffuse, soft hypertrophy of the thyroid; pulse 80 to 90; palpitation occasionally; no weight or strength had been lost.

This case was selected for study on account of the recent onset and consequent possible greater sensitiveness to hormone treatment. A greatly increased diet, supplying 55 calories per kilogram was given during the entire period of observation. On this diet, combined with

TABLE 5.—M. F. EXOPHTHALMIC GOITER

Period	Date	Change in Weight, lb. oz.	N Intake, Gm.	N in Urine, Gm.	N in Feces, Gm.	N Balance, Gm.	Medication	Diet			
								Prot., Gm.	Fat, Gm.	Carb., Gm.	Cal.
1	8/12-18	+ 10	16.17	11.37	1.83	+2.97	0	104	153	353	3,317
2	8/19-25	— 4	16.49	10.87	2.85	+2.77	0.01 mg. H. I.				
3	8/26-9/1	— 4	16.30	11.71	1.76	+2.81	0.01 mg. H. I.				
4	9/2-8	+1 0	16.82	11.59	1.70	+3.61	0.005 mg. H. I.				
5	9/10-16	+ 2	16.52	11.25	1.97	+3.30	0.02 mg. H. I.				
6	9/17-23	+ 2	16.47	11.57	1.73	+3.17	0				
7	9/24-30	+ 2	16.46	12.27.	1.94	2.25	0				

rest and quiet, M. F. became rapidly less nervous and excitable before the hormone was administered. An increased nitrogen balance was obtained in Periods 3, 4 and 5 with hormone administration. There seemed in this case to be no definite relation between the amount of nitrogen retained and the thyroid dosage. The clinical condition continued to improve during the entire course of the metabolic study. The pulse decreased in rate to normal, the thyroid swelling grew somewhat less, and the mental state improved. We were, however, unable to trace any definite relationship between a given dosage of the hormone and the clinical improvement. The doses of hormone in this case were minimal, no toxic symptoms having been observed at any time.

CASE 6.—J. H., man, aged 31, Finn, a carpenter by trade. Diagnosis, exophthalmic goiter. Two brothers and one sister have or had goiter. The sister's eyes were protuberant. One brother recovered after the goiter had been removed. For the previous three years J. H. had been incapacitated by weak-

ness and nervousness. On account of his poor condition palliative ligation of the superior thyroid arteries was performed by Dr. J. Prescott Grant of the New York Polyclinic Hospital, to whose courtesy I am indebted for this case. Operation was followed by improvement for some time. His weight in 1915 was 172 pounds; on admission Aug. 31, 1916, it was 118 pounds.

Examination.—Extremely nervous expression; patient thin and weak; musculature poor; twitching of facial muscles; choreiform movements and marked fine tremor of hands; nails thin and seamed; atrophic skin patches; tremor of tongue; teeth defectively calcified; large pulsating thyroid of great density; right lobe large; bruit present; circumference of neck 40 cm.; left cardiac border 10 cm. from midsternum; no murmurs; pulse 110 to 120, quick and easily compressible; urine negative.

TABLE 6.—J. H. EXOPHTHALMIC GOITER

Period	Date	Change in Weight, lb. oz.	N Intake, Gm.	N in Urine, Gm.	N in Feces, Gm.	N Balance, Gm.	Medication	Diet			
								Prot., Gm.	Fat, Gm.	Carb., Gm.	Cal.
1	9/4-9*	— 10	14.93	9.15	2.23	+3.55	0	91	122	434 (9/4-22)	3,069
2	9/16-22†	— 6	14.92	9.19	2.22	+3.50	0.01 mg. H. I.				
3	9/25-29	—2	8.83	8.88	1.21	—1.26	0	54	60	272 (9/23-10/6)	1,806
4	9/30-10/6†	— 6	8.86	8.99	1.43	—1.56	0.01 mg. H. I.				
5	10/9-15	—1	11.78	10.28	2.00	—0.49	0	72	100	335 (10/7-11/10)	2,566
6	10/16-22	+ 4	11.78	10.38	1.49	—0.09	0.02 mg. H. I.				
7	10/23-29	+1 10	11.78	8.84	1.75	+1.19	0.02 mg. H. I.				
8	10/30-11/5	+ 4	11.75	8.33	1.68	+1.74	0.03 mg. H. I.				
9‡	11/6-10†	+1 8	11.81	8.72	2.26	+0.82	0.03 mg. H. I.				
10	11/16-22	+1 4	15.16	9.42	2.26	+3.48	0	94	96	404 (11/11-12/14)	2,891
11	11/23-29§	+ 4	15.22	9.95	1.90	+3.37	0.02 mg. H. I.				
12	12/7-13	.....	15.25	8.09	1.94	+4.61	0.02 mg. M. I.				

* September 10-16, balance omitted; diet unchanged.
† On the following days, 9/22-25; 10/6-9; 9/10-16, the balance was omitted to allow the change of diet to have its effect.
‡ Five day balance; patient became toxic.
§ November 30 to December 6, balance omitted; diet unchanged.

This severe case proved a very enlightening study. His state of increased metabolism was well demonstrated in the first two periods (see protocols) where he showed a tendency to lose weight on a diet supplying 3,069 calories, or 57 calories per kilogram. The first four periods are chiefly interesting dietetically, the nitrogen balance remaining practically unchanged by the minimal amount of hormone administered. In Periods 6, 7 and 8 an increased dose of hormone 0.02 and 0.03 mg. H. I. daily) caused a decided increase in the nitrogen balance until the patient developed slight toxic symptoms, tachycardia and nervousness in Period 9, with a resulting decline in the balance. The nitrogen balance was again increased in Period 12 with a dose of 0.02 mg. H. I. daily.

This patient's clinical condition became markedly improved during his stay in the ward, but here again it was not possible to trace any definite relation between the thyroid medication or its absence to this improvement.

The clinical improvement consisted in a gain in strength, decrease in size of goiter, from 40 cm. on [illegible]31, 1916, to 37.5 cm. on Dec. 15, 1916, together with marked change to a softer consistency. The blood Sept. 5, 1916, showed hemoglobin, 65 per cent.; erythrocytes, 3,900,000; white blood cells, 13,000; neutrophils, 60; small lymphocytes, 34 per cent.; large lymphocytes and mononuclears, 6 per cent. After treatment, hemoglobin, 87 per cent.; erythrocytes, 5,200,000; white blood cells, 9,400; eosinophils, 2 per cent.; neutrophils, 56 per cent.; small lymphocytes, 13 per cent.; large lymphocytes and large mononuclear cells, 20 per cent.; transitionals, 1 per cent.

TABLE 7.—J. W. EXOPHTHALMIC GOITER

Period	Date	Change in Weight, lb. oz.	N Intake, Gm.	N in Urine, Gm.	N in Feces, Gm.	N Balance, Gm.	Medication	Diet			
								Prot., Gm.	Fat, Gm.	Carb., Gm.	Cal.
1	11/10-14	— 12	21.42	17.82	1.68	+1.91	None	135	208 (1/29-4/5)	204	3,400
2	11/15-19	— 6	21.15	16.10	1.45	+3.59	None				
3	11/20-27	—1	21.34	15.79	1.54	+4.00	0.02 mg. H. I.				
4	11/28-3/6	— 8	21.39	15.29	1.50	+4.60	0.06 mg. H. I.				
5	3/1-13	— 4	21.31	14.89	1.63	+4.70	0.06 mg. H. I.				
6	3/14-20	+ 4	21.40	14.80	2.06	+5.29	0.01 mg. H. I.				
7	3/21-27*	— 2	21.38	14.48	1.83	+5.07	0.11 mg. H. I.†				
8	3/31-4/5‡	± 0	21.38	14.76	1.90	+4.72	0.22 mg. H. I.† 0.44 mg. H. I.†				
9	4/10-16	+ 12	13.66	11.97	2.00	−0.31	None	80	86 (4/6-30)	227	2,070
10	4/17-23	± 0	13.69	11.13	2.00	+0.56	None				
11	4/24-30‡	— 6	13.66	11.38	1.61	+0.67	None				
12	5/6-11	+ 4	14.50	10.11	1.63	+2.76	None	86	188 (4/31-5/6)	280	3,247
13	5/12-18	+ 8	14.48	9.64	1.53	+3.31	None				
14	5/19-24	+ 4	14.44	9.80	1.46	+3.09	None				

* March 28-30, balance omitted; diet unchanged.
† Armour's tablets given, H. I. calculated.
‡ On the following days, 4/6-10; 4/31-5/5; the balance was omitted to allow the change of diet to have its effect.

CASE 7.—J. W., man, aged 35 years, Hebrew, painter by trade. Diagnosis, exophthalmic goiter, mitral insufficiency, quiescent pulmonary tuberculosis. The patient had a history of institutional treatment for tuberculosis in 1912; exophthalmic goiter symptoms since 1916, also swelling of ankles and dyspnea. Examination on admittance Jan. 25, 1917, disclosed exhaustion, emaciation, irritating cough, tremor of hands and tongue, abnormal perspiration, dermographia, cutaneous atrophy, nervous expression of face, marked exophthalmos, the special ocular signs, moderate-sized goiter, tachycardia (100 to 120), slight cardiac enlargement to left, systolic mitral murmur, signs of old apical tuberculosis of right lung, no râles, splenic enlargement, liver 3 cm. below costal margin, slight dorsolumbar scoliosis. The urine occasionally showed sugar, discovered in 1916. Blood pressure and blood were normal; nonprotein nitrogen 39.6 mg., and uric acid 2.6 mg. per 100 c.c. blood.

There was a distinct increase in the nitrogen balance with thyroid medication until the patient was made toxic in Period 8 with a consequent decline in the retention. The latter part of the experiment (Periods 9 to 14) was devoted to observations on the effect of different diets on the patient's condition (see special section).

The clinical condition of this patient became much improved as a result his stay in the ward. The weakness and ocular symptoms grew less, nervousness and the pulse-rate decreased and the cough subsided. The goiter, however, remained quite unchanged.

Conclusions from the Exophthalmic Goiter Experiments. — The impression gained from this work is not encouraging from a therapeutic standpoint, although the cases improved generally while under observation. In one severe case (J. H.) the patient grew strikingly better. These results, however, may just as likely have been due to the effects of rest, better diet and hygienic environment as to the minute amounts of the thyroid hormone administered. The symptoms of toxicity exhibited on such doses do not indicate any possibility that the hormone acts in any way differently from other thyroid preparations in these toxic cases. It is, however, remarkable that in spite of the known tendency to nitrogen loss in exophthalmic goiter, the nitrogen balance became increased when 0.02 mg. H. I. was administered. A possible explanation of this result is reserved for the general discussion.

VII. DIET IN THYROID DISEASE

Diet in Hypothyroidism.—In this condition the following facts have been clearly established by previous investigation. The basal metabolism is markedly decreased. Equilibrium is maintained on a diet supplying fewer calories than normal requirement. Few attempts at dietary studies have been made. We therefore subjected our cretin to various dietetic régimes in an effort to determine which ration is most suitable for this condition.

The effect of a high caloric mixed diet was first tried. (Protocol Period 1.) Although this diet supplied 50 calories per kilogram, the patient lost weight. Her clinical symptoms during this time remained unchanged. A high protein diet of approximately the same caloric value (Period 13) supplying 46 calories per kilogram, caused a considerable retention of nitrogen, but the patient's general condition was not as satisfactory as on the mixed diet. A negative nitrogen balance resulted in Period 10 on a diet supplying nearly as many calories (42 cal. per kg.) and containing a very low protein content, but with approximately the same amount of carbohydrate and fat as was in the high protein diet. Finally a mixed diet of much lower caloric value (31.4 cal. per kg. in Period 21), although not sufficient in itself to

prevent loss of weight, was found to prove very satisfactory for the cretin's needs when taken in conjunction with a therapeutic dose of hormone.

According to Falta, in myxedema "the protein requirements are light, and there may be an addition of protein to the body." Our results for cretinism do not bear out this statement that nitrogen is more easily retained. Indeed, the reverse is probably true; otherwise additional nitrogen would not be retained when optimal doses of thyroid are administered, as took place in our experiments.

What practical deductions can be drawn from these data? It is evident that (1) in cretinism just as in the case of normal individuals a high protein or a high carbohydrate diet is less advantageous than a mixed diet containing rationally balanced amounts of carbohydrate, protein and fat; (2) diets supplying increased calories do not avail to improve the clinical condition, the reason being that in this disease only a reduced amount of food can be assimilated by the untreated cretin, the remainder of the food being excreted. The amount of food ingested should be gradually increased as the thyroid treatment yields results. Cretins should therefore be maintained on a liberal mixed diet, without attempts at forced feeding.

Diet in Hyperthyroidism.—The majority of older observers favor the use of a low protein diet in this disease. The few metabolic experiments made with patients do not, however, substantiate this view. This point is clearly brought out by the experiments of Pribram and Porges,[6] who found the respiratory quotient of this disease unchanged by a low protein, high carbohydrate diet and very properly deduced that the essential condition of these patients remained, therefore, unimproved. On the other hand, a high protein diet with restriction of the carbohydrates, but supplying the same number of calories, produced an increase in the basal metabolism and a loss of weight. The best results were obtained with a mixed diet. Du Bois[7] in a recent series of exact experiments found that rather less than a normal amount of carbohydrate is consumed in metabolism in these cases. On the other hand, data bearing on this point were reported in the immediately preceding article[8] in which it was shown that the carbohydrate exerts its sparing effect in preventing nitrogen loss in experimental hyperthyroidism. This result is important as it indicates that a certain, but not necessarily predominant amount of carbohydrate in the diet of hyperthyroid cases is useful in combating the nitrogen loss.

6. Pribram, E., and Porges, O.: Wien. klin. Wchnschr., 1908, **46**, 1584.
7. Du Bois, E. F.: THE ARCHIVES INT. MED., 1916, **17**, 915.
8. Janney, N. W., and Isaacson, V. I.: The Effect of Thyroidectomy and Thyroid Diseases on the Protein Metabolites, in this issue.

Our present experiments represent an extension of these investigations. A study of the protocols of the exophthalmic goiter cases shows that the high caloric diet is essential to prevent further loss of weight when weight was being lost. The nitrogen loss in the feces was large, greater than can be accounted for by the increased diet given. This, together with the excessive amounts of the fats frequently found in the dejecta, points to defective intestinal absorption in this condition.

The most favorable diet was found to be one in which the protein, fat and carbohydrate are present in the usual proportions, but in increased amounts. This is well exemplified by the following dietary study.

CASE 8.—E. T., man, aged 34, Swiss, collector by trade, was referred by courtesy of Dr. John Rogers and Dr. Eugene F. DuBois of the Cornell Medical School. Since 1915 he had been incapacitated with weakness, loss of weight, dyspnea, and diarrhea. On December 31 he was operated on by Dr. Rogers

TABLE 8.—E. T. EXOPHTHALMIC GOITER

Diet	Diet					Change in Weight, Lb. Oz.	N Balance, Gm.	Remarks
	Prot., Gm.	Fat, Gm.	Carb., Gm.	Calories	Calories per Kg.			
12/ 9-12	95	106	356	2,700	49.6	—1 6	+0.80	
12/13-17	95	137	379	3,218	59.6	± 0	+1.94	Diet unchanged 12/13-1/9
1/14-20	104	211	378	3,942	73.7	+ 6	+3.90	Diet unchanged 1/9-11/3

by ligation of the superior thyroid arteries and removal of tips of both lobes. Improvement followed. He was admitted to the metabolism ward of the Montefiore Hospital, Dec. 1, 1916. The patient exhibited some emaciation, a tendency to flushing and perspiration, slight tremor, exophthalmos, von Graefe's sign, dermographism and a thyroid of normal size but indurated to touch. The left border of the heart was 11.5 cm. from midsternum; there was a systolic mitral murmur; temperature normal; respiration 20 to 24; pulse 100; blood count and differential normal.

The dietary studies of this moderately severe case of exophthalmic goiter are abstracted in the table. The patient was under observation in the metabolism ward under the precise conditions described in the preceding pages, with careful estimation of the nitrogen balance. It is seen that weight was lost on a diet quite sufficient to cause a gain in a healthy person (Period 1). A mere increase in the carbohydrate and fat and consequently in the number of calories was sufficient to prevent loss of weight and also to bring about a distinct gain in the nitrogen balance (Period 2). On a still higher caloric mixed diet (Period 3) the weight began to rise and nitrogen was retained in greatly increased amounts.

These results correspond well to previous studies made by Dr. Du Bois on the same patient in January, 1915. He found the weight to remain stationary but the nitrogen balance to be markedly positive on a mixed diet of 2,452 to 2,605 calories, which was from 59 to 62 calories per kilogram.

Evidently the dietetic treatment of exophthalmic goiter presents no mysteries. Neither a high protein nor a high carbohydrate diet is followed by as good results as is a mixed diet of adequate caloric value. The same general rules of nutrition hold good in exophthalmic goiter as in the case of normal persons.

VIII. GENERAL DISCUSSION

The studies here reported belong to a series of researches aiming at a better understanding of thyroid function in health and disease. Growing out of this work and an extensive critical literary review made necessary by it, several changes in point of view have been reached, which will now be developed.

The general belief in the past with regard to thyroid function, has been that this gland acts normally as a stimulant to metabolism, especially to the protein metabolism. To use the words of von Noorden, the thyroid "stimulates metabolism like a bellows fans a fire." This view has been based on the following points: (1) Ingestion of thyroid material leads to increased metabolism and loss of nitrogen. (2) Myxedema and cretinism are characterized by a general decrease in metabolism, especially by a low gaseous exchange and nitrogen output, which is ascribed to "a lack of the stimulatory effect of the thyroid on metabolism." (3) Exophthalmic goiter is similar to the effects of a large overdose of thyroid substance and is therefore accepted as clinical phenomena due to "hyperthyroidism." A careful scrutiny of the known data has, however, made it very doubtful whether the thyroid problem can best be accounted for in so simple a manner. Our points of view will now be developed in detail.

1. *Anabolic and Catabolic Actions of the Thyroid.*[9]—There must be considered the influence of the thyroid on metabolism both in health and disease. It is a well established fact that the usual effect of thyroid taken by normal individuals is loss of nitrogen from the body, sometimes loss of weight, and an increased general metabolism. There exists excellent evidence, however, that under certain circumstances the thyroid can exert practically the opposite effect.

Recent experiments by Schafer[10] and Hewitt[11] have afforded valu-

9. These views were originally advanced by the writer in December, 1916, at the Annual Meeting of the American Society of Biological Chemists.

10. Schafer, E. A.: Quart. Jour. Exper. Physiol., 1912, **5**, 203.

11. Hewitt, J. A.: Quart. Jour. Exper. Physiol., 1914, **8**, 297.

able data. These authors fed thyroid gland to white mice in varying amounts and studied the nitrogen metabolism and body weight. The following condensed tabulation has been compiled and calculated from Hewitt's second article. These experiments were evidently carefully carried out and the fecal nitrogen was also controlled.

From the tabulation it is evident that the *amount* of thyroid gland administered determines its effect on metabolism. The feeding of 0.25 gm. daily in the second week caused a slight loss in body weight, with a decided decrease in the nitrogen retained. In other experiments the feeding of 0.5 and 1.0 gm. under the same conditions led to still greater loss of weight and nitrogen. When, however, 0.125 gm. daily was administered, more food and nitrogen were ingested than under normal dietary conditions or when a larger amount of gland was fed.

HEWITT'S THYROID FEEDING EXPERIMENTS

Week	Diet	Food per Kg., Gm.	Nitrogen Intake per Kg., Gm.	Nitrogen in Urine, per Cent.	Nitrogen Retained per Kg., Gm.	Gain or Loss in Weight, per Cent.
1	Normal period	261	2.66	1.55	1.36-7	7.0
2	0.25 gm. oxythyroid daily.....	253	2.56	2.06	1.14	1.7
3	0.125 gm. oxythyroid daily.....	305	3.36	2.09	1.61	10.4
4	0.25 gm. oxythyroid daily.....	304	3.20	2.11	1.35	2.3

The urinary nitrogen remained stationary. It is, however, very significant that 18 per cent. more nitrogen was retained than in the normal period and that the body weight increased 10.4 per cent. corresponding to about 50 per cent. over and above the total increase noted in the normal period for the same length of time.

Experiments with similar results have been recorded by Fonio[12] for myxedema patients. Minimal amoumts of thyroid compounds caused a gain in nitrogen retention while greater amounts caused loss. These experiments are subject to criticism on technical grounds.

To understand the significance of these findings one must bear in mind that the thyroid is scarcely second to the hypophysis in exerting a stimulating influence on growth. Abolition of thyroid function in the very young leads to stunted growth (cretinism). Proper thyroid medication causes growth to be resumed. Cessation of thyroid medication is followed by cessation of growth. Experiments carried out on tadpoles illustrate the stimulating effect of the thyroid on growth, as metamorphosis into frogs is greatly accelerated by thyroid feeding.[13]

12. Fonio, A.: Mitt. a. d. grenzgeb. d. Med. u. Chir., 1912, **24,** 123.

13. Gudernatsch, J. F.: Arch. Entwickl., 1912, **35,** 457; Citronei, G.: Arch. ital. biol., 1914, **61,** 305.

The part played by the nitrogen metabolism in relation to growth is quite well known. A pronoumced gain of nitrogen on a proper diet is usually to be regarded as a sign of increased regeneration of tissue or actual growth, for which the nitrogen "gain" of childhood is a good example. *Hence it is evident that a therapeutic action of the thyroid should be found to be accompanied by a gain, not a loss, of nitrogen.*

In the present article we have seen how small doses of thyroid suffice to cause clinical improvement in a cretin, which changes were accompanied by an *increased retention of nitrogen.* These experiments were so carefully carried out that we believe them acceptable proof that an increase in the nitrogen balance is an indication of the therapeutic, or anabolic, effect of the thyroid.

But how, then, account for the increased protein metabolism, that is, the increased output of nitrogen following thyroid medication, which is usually accredited to thyroid action? Further investigation and reflection have led us to the conviction that in such cases we are dealing with a toxic rather than a therapeutic effect of the thyroid material and that the loss of nitrogen is very probably a toxic loss.[14]

Our present control experiments have shown that the loss of nitrogen may be caused by the slightest overdose of thyroid without necessarily being accompanied by clinical toxic symptoms. Hence it is easy to understand how in the past the thyroid became regarded as normally stimulatory to metabolism.

The thyroid is probably capable of exerting an effect on each cell of the organism (Plummer) by influencing specifically certain metabolites. Among them are to be ranked the carbohydrates and purins, as previous studies[8] of this series have shown. Experiments by Kendall point to the amino-acids as being directly affected by the thyroid hormone. The carbon-dioxid output is also increased. All these observations emphasize that fundamental changes in the intermediary and basal metabolism are caused by the thyroid whether acting constructively or destructively on tissue, as Bensley's[15] experiments on opossums illustrate. It is entirely possible that this function is accomplished by a selective action on certain articles of the diet through intermediary changes which are at present obscure.

The clear recognition that nitrogen loss following thyroid medication is a toxic manifestation is of practical importance in the thyroid treatment of obesity. It is well known that a rapid loss of weight is to be attained by the use of thyroid tablets in such cases. The malaise

14. The view that the loss of nitrogen following thyroid medication in myxedematous subjects is due to the dissolution of the myxedematous tissue remains an hypothesis without the foundation of experimental proof.

15. Bensley, R. R.: Am. Jour. Anat., 1916, **19**, 37.

and weakness which are sometimes exhibited are, however, doubtlessly clinical symptoms of a toxic effect caused by the thyroid as they are accompanied by loss of protein tissue as well as the desired loss of fat. In view of our studies, the use of thyroid in uncomplicated cases of obesity cannot be recommended. I reserve its use, in small doses, to the not uncommon cases of obesity due to thyroid hypofunction.

2. *Metabolism in Hypothyroidism.*—Cretin metabolism is usually characterized in the literature as being "träge" or inactive ever since the time Magnus-Levy made the remarkable discovery that the basal metabolism is greatly depressed in this condition. Protein metabolism is also regarded as much "reduced"; that is, much less nitrogen and nitrogenous substances in general are excreted. These effects are ascribed to the "absence of the stimulatory effect of the thyroid on metabolism." Statements are also made in the textbooks that in cretinism nitrogen is readily retained, that is, protein built up in the body.

Let us now critically study these conceptions. There can be no doubt of the reduction of general metabolism in cretinism as the careful experiments by Du Bois,[7] using the modern calorimeter, have amply demonstrated. In cretinism little food is taken, with consequent decreased elimination of nitrogen. The reason for this is probably as follows. Only reduced amounts of food can be properly assimilated by the organism, therefore the reduction of intake. That this is true is evident when a cretin is put on a greatly increased diet having abundant protein, as in our case. The increased food fails to be used in tissue repair and upbuilding, with resultant growth such as takes place normally under these circumstances. In consequence *more* nitrogen is actually lost than in the case of a normal person on the same diet. An increased amount of nitrogen is retained with improvement of the clinical symptoms on the same diet when thyroid is administered in proper dosage. Coincidently the basal metabolism rises to normal owing very probably to the increased assimilative and anabolic processes which may likewise necessitate an increased oxygen intake and carbon dioxid output. *It may then be concluded that the depressed nitrogen excretion in cretinism is not due to "absence of stimulatory effect," but rather to the failure of normal repair and growth processes which are controlled by the thyroid. As these constructive processes are inhibited, little food is taken, for more cannot be assimilated. A low nitrogen output results.* The decreased nitrogen excretion and lowered gaseous metabolism are probably to be accounted for as the result of a compensatory and sparing effort on the part of the human economy, for there are various other examples of like nature known, that is, the mineral metabolism, in which the organism shows a marked ability to conserve necessary materials when they cannot be properly replaced from without.

For the statement that "cretins show a tendency to retain nitrogen easily," we find no experimental proof in an exhaustive study of the pertinent literature. Our experiments clearly show quite the opposite. Indeed, common sense would make it seem impossible that a cretin who suffers from inability to grow, should more easily retain nitrogen, that is, presumably build protein more readily than a normal child. The basis for this false idea is probably that such hypothyroid conditions have been in the past simply regarded as the direct antithesis of hyperthyroidism, in which increased breakdown of protein is well known to occur.

Magnus-Levy and others[16] have accounted for the decreased metabolism of hypothyroidism on the basis of a decreased alimental absorption due to sluggishness of the intestinal tract. Here again, substantiating experimental evidence has been lacking. In a previous research[5] we have therefore investigated this possibility by means of the nitrogenous excretion. We found no delay in intestinal absorption to follow thyroidectomy in animals. Pari[17] has made similar observations. Additional data covering this point is afforded by our cretin experiments. A study of these protocols makes it clear that the absorption of food, as shown by the nitrogen of the feces, was quite good throughout, demonstrating that the intestinal functions were not disturbed.

The chief difficulty with food assimilation in cretinism evidently lies in the inability of the body to make adequate use of the nitrogenous and probably other food material *after* absorption. The effect of the thyroid medication on the urinary nitrogen (see protocols) gives a clear insight into this. When the dose was therapeutic, definitely less nitrogen was excreted in the urine than without treatment on the same diet. The fecal nitrogen, meanwhile, was not obviously affected. Evidently in their passage through the blood and tissues of the body, more nitrogenous metabolites are retained for constructive purposes as an effect of thyroid treatment.

Cretins and myxedematous individuals are characterized by abnormal adiposity, the deposits sometimes occurring in unusual locations of the body. In seeking an explanation for this metabolic change, attention may be called to our recent studies[5] on thyroidectomized animals in which a decreased assimilability for sugar was demonstrated. One of the first evidences of a disturbance in carbohydrate metabolism is a tendency to adiposity. Fifty per cent. of diabetics are or have been adipose. It seems, therefore, logical to presume that the fat deposits of the hypothyroid conditions are related in origin to the disturbance in carbohydrate metabolism. This view is substantiated

16. Magnus-Levy, A.: Von Noorden's Handbuch d. Path. des Stoffwechsels, Berlin, 1907, p. 335.
17. Pari, G. A.: Biochem Ztschr., 1908, **13**, 274.

by extended metabolic studies carried out by us on muscular dystrophy,[18] in which disease abnormal fat depositions are not uncommon, and a similar disturbance in carbohydrate metabolism was found to occur. The reduction of fat in hypothyroid cases undergoing thyroid treatment is not necessarily due to a direct effect of the ingested thyroid on the combustion of the fat, but very possibly is a result of the general

TABLE 9.—Specimen Daily Protocol (S. M., Control)

Diet: Protein, 77 gm.; Fat, 87 gm.; Carbohydrate, 245 gm.; Calories, 2,111

Period	Date	N Intake, Gm.	N in Urine, Gm.	N in Feces, Gm.	N Balance, Gm.	Medication
	1916					
3	7/23	12.14	8.91			
	7/24	12.14	8.64			
	7/25	12.14	8.94			
	7/26	12.19	9.64	6.67	+13.56	None
	7/27	12.19	9.63			
	7/28	12.14	9.59			
	7/29	11.35	8.71			
4	7/30	10.71	7.98			
	7/31	12.14	8.71			
	8/ 1	12.14	9.20			
	8/ 2	12.14	9.17	5.93	+17.67	None
	8/ 3	12.14	8.65			
	8/ 4	12.14	8.63			
	8/ 5	12.14	7.61			
5	8/ 6	12.14	8.20			
	8/ 7	12.14	8.86			
	8/ 8	12.14	8.41			
	8/ 9	11.44	9.50	6.41	+16.96	0.38 gm. gland
	8/10	12.14	9.54			
	8/11	12.16	7.93			
	8/12	12.15	9.50			
6	8/13	12.14	8.75			
	8/14	12.14	9.21			
	8/15	12.30	8.69			
	8/16	12.30	9.69	7.72	+10.41	0.38 gm. gland
	8/17	12.00	9.29			
	8/18	10.48	9.42			
	8/19	12.08	10.26			
7	8/20	12.18	9.71			
	8/21	12.16	8.92			
	8/22	12.16	9.62			
	8/23	12.17	8.86	10.89	+9.89	5 mg. H. I.
	8/24	12.14	9.25			
	8/25	12.15	8.96			
	8/26	12.14	9.00			
8	8/27	12.20	8.94			
	8/28	12.19	9.74			
	8/29	12.14	8.83			
	8/30	12.19	7.93	5.97	+17.65	None
	8/31	12.20	9.08			
	9/ 1	12.20	8.38			
	9/ 2	12.20	8.83			

readjustment of metabolic processes, which are secondary to the anabolic and constructive effects of the administered glandular preparations.

3. *Pathogenesis of Exophthalmic Goiter. Criticisms of the Hyperthyroid Theory.*—Ever since Kocher published his classic tables con-

18. Janney, N. W., Goodhart, S. P., and Isaacson, V. I.: The Archives Int. Med., 1918, **21,** 188.

trasting the symptoms of hypothyroidism with hyperthyroidism, the conception of "hyperfunction" has been held by most observers to account for exophthalmic goiter. A survey of the evidence, however, some of recent date, renders the acceptance of this view very difficult. These criticisms will now be alluded to in detail.

On *a priori* grounds: When, as in cardiac hypertrophy, increase in the functional activity of an organ occurs, there is always an evident need for the increased activity. The only apparent exception to this rule seems to be acromegaly, but in this condition degenerative processes accompany or soon follow on the overgrowth.

Although the hyperfunctional theory would seem to find a basis in the hyperplasia and hypertrophy found in the great majority of the glands from Graves' disease patients, the exhaustive studies by Wilson[19] and Plummer[20] of the rich material of the Mayo Clinic, have emphasized the presence of a considerable "toxic nonhyperplastic" group of cases, presenting a variable histopathology, sometimes degenerative in type. Again, until more is known of the metabolism of thyroid secretion the doubt must remain whether the patches of hypertrophy and hyperplasia found in toxic goiters does not represent a compensatory effort at regeneration of a functionally incapacitated gland. It must also be remembered that certain hyperplastic adenomas of the thyroid are notably nontoxic.

Even the typical exophthalmic goiter contains but $\frac{1}{50}$ to $\frac{1}{20}$ of the total active *a*-iodin present in normal thyroids, according to Kendall and Wilson.[21] If the hyperthyroid hypothesis were correct, more, not less, iodin should be present in such hyperfunctioning thyroids. Explanations of this discrepancy have been made, but none are supported by good evidence.

Haseman and Walter found that normal thyroid tissue implanted into thyroidectomized rabbits was followed by normal degeneration and regeneration of crushed nerve fibers, which processes took place much more slowly, if at all, when Basedow tumor tissue was thus engrafted. I have, however, been unable to find an accurate description of these striking experiments, which would indicate a lowered functional condition of the exophthalmic goiter and aptly illustrate the part played by the thyroid in the regeneration of tissue.

Exophthalmic goiter is not infrequently found in families having hypothyroid members. The combination of toxic exophthalmic goiter symptoms with hypothyroidism has been frequently observed in the same person. According to Bertine[22] of the Cornell Medical School

19. Wilson, L. B.: Am. Jour. Med. Sc., 1913, **146,** 781.
20. Plummer, H. S.: Am. Jour. Med. Sc., 1913, **146,** 790.
21. Wilson, L. B., and Kendall, E. C.: Am. Jour. Med. Sc., 1916, **151,** 79.
22. Bertine, E.: Med. Rec., New York, Nov. 18, 1916.

Clinic, they are present in 23 per cent. of thyroid cases. This close association of hypothyroid and hyperthyroid symptoms is strongly indicative that the same general cause is present in both conditions. As cretinism and myxedema are unquestionably due to thyroid deficiency, it is likewise probable, in view of the reasons just mentioned, that the thyroid does not function adequately in exophthalmic goiter. Ochsner[23] in an admirable surgical article on hyperthyroidism, concludes that this condition in adolescents is due to growth of the breasts and skeleton at this time, and is comparable to the hyperthyroidism of pregnancy. The large number of "hyperthyroidism" cases developing among army recruits during the training period may likewise be mentioned.[24] Such conditions are therefore to be regarded rather as dysfunctional in nature, caused by an overstrain on the gland.

Cases of exophthalmic goiter without tumor are not so very uncommon, which fact is contrary to the hyperthyroid theory. In other cases the tumor recedes but the toxic symptoms continue. Although thyroid medication usually makes exophthalmic goiter patients worse, cases[25] have been persistently reported in which the patients have derived benefit from this treatment. This is one of the strongest arguments against the hyperthyroid theory.

Factors which act in lowering the general resistance of the body or of the thyroid are active in the production of exophthalmic goiter. Such are acute thyroiditis, acute infectious fevers and shock. It seems unreasonable that these depressant conditions could produce increased functional activity of any organ including the thyroid.

Similar metabolic disturbances are present in both hyperthyroid and hypothyroid conditions. Thus, the blood sugar tolerance test shows a delayed curve in both instances.[5] Hypoglycemia, a symptom of hypothyroidism, is sometimes present in exophthalmic goiter.[26] Creatin is present in the urine of both hyperthyroidism and hypothyroidism.

The blood picture of exophthalmic goiter (characterized by reduction of the neutrophils, lymphocytosis and mononucleosis[27]) is practically identical with that of myxedema and cretinism.[28] If these con-

23. Ochsner, A. J.: Ann. Surg., 1916, **64,** 385.

24. Verbal communication of Major Harlow Brooks, M. R. C., Camp Upton.

25. Murray, G. R.: Twentieth Century Practice of Medicine, New York, 1895, **4,** 804; Buschau, G.: Basedow'sche Krankheit, Leipzig, 1894; Strumpell, A.: Textbook of Medicine, New York, 1911, p. 581.

26. Writer's observation.

27. Caro, L.: Berl. klin. Wchnschr., 1908, **45,** 1755; Kocher, Th.: Arch. f. klin. Chir., 1908, **87,** 131; Klose, H., Lampe, A. E., and Lisegang, R. E.: Beitr. z. klin. Chir., 1912, **77,** 601.

28. Klose, H.: Ergebd. inn. Med. u. Kinderh., 1913, **10,** 167; Fonio, A.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1912, **24,** 123.

ditions are diametrically opposed, such a striking similarity in the metabolic and hematologic picture would scarcely be found.

The foregoing considerations seem sufficient to show the inadequacy of the hyperthyroid theory of exophthalmic goiter to account for the known facts.

THE HORMONE HYPOTHESIS OF THYROID TOXEMIA AND EXOPHTHALMIC GOITER

If we then discard the hyperthyroid theory, we have but one remaining explanation, "dysfunction" of the thyroid as the cause of exophthalmic goiter. The difficulty has been to formulate any view of the pathogenesis of exophthalmic goiter on a dysfunctional basis which is not open to serious criticism. The hypothesis which will now be developed has slowly matured. It seems to explain most of the facts fairly adequately in view of present knowledge. It is, however, fully recognized by me that it, too, lacks proof. It has value merely as a working hypothesis until future researches either prove or disprove its usefulness.

The most convincing argument in favor of the hyperthyroid theory has been the fact that the ingestion of large amounts of thyroid preparations leads to toxic symptoms, even including exophthalmos, which may become identical with the disease exophthalmic goiter.[29] Several other well authenticated cases are known.

The facts, then, are these: Many or all the toxic symptoms of Graves' disease may appear in connection with (1) pathologic changes in the thyroid gland; that is, exophthalmic goiter; (2) as a result of administration of thyroid material *or thyroid hormone* in excess to normal, myxedematous or thyroidless human beings, or animals. A logical consideration of this situation leads to the deduction that the thyroid hormone itself is capable, in overdose, of producing the toxic phenomena accompanying exophthalmic goiter, as it produces this effect both in the presence of nonfunctioning thyroids or in the entire absence of this gland from the body. The experiments of Kendall and myself, in which we observed the symptoms of hyperthyroidism from the injection of overdoses of thyroid hormone, afford still more definite evidence in this regard. We have, therefore, to seek the toxic causative agent in the thyroid hormone.

The toxic manifestations require a latent period of from twenty-four to forty-eight hours for their development (Kendall, Janney), which time may be required for the changes to take place in the hormone itself before symptoms are produced. It is likely that the hormone, when present in the body in excess, is subject to the general laws

29. Notthafft, v., A. F.: Zentralbl. f. inn. Med., 1898, **19**, 353.

of catabolism, just as is any related cyclic chemical substance provided with a side chain. Such an example is the normally occurring amino-acid, tryptophane, likewise containing the indol group, which yields in the intestine the putrefactive products indol and skatol. Chemically

TABLE 10.—SPECIMEN DAILY PROTOCOL (Y. K., CRETIN)

Period	Date 1916	N Intake, Gm.	N in Urine, Gm.	N in Feces, Gm.	N Balance, Gm.	Medication	Remarks
1	3/13	10.54	8.47	3.25			
	3/14	10.54	7.90				
	3/15	10.55	8.41				
	3/16	10.53	9.88	0.88	+9.70	None	(For diets see Table 4)
	3/17	10.54	7.75	1.27			
	3/18	10.54	7.74	1.35			
	3/19	10.54	7.18				
2	3/28	10.54	6.84	1.50			
	3/29	10.54	6.98	1.02			
	3/30	10.56	6.67	0.58			
	3/31	10.54	7.29	1.70	+16.99	0.5 gm. gland	
	4/ 1	10.52	7.65	0.70			
	4/ 2	10.54	6.62	1.37			
	4/ 3	10.54	7.40	0.47			
3	4/ 4	10.54	7.44	0.93			
	4/ 5	10.54	7.21	1.41			
	4/ 6	10.52	7.19	0.31			
	4/ 7	10.56	6.70	0.79	+18.37	0.5 gm. gland	
	4/ 8	10.54	6.70	0.78			
	4/ 9	10.54	6.76	2.15			
	4/10	10.54	6.64	0.40			
	6/ 4	.....	....	....	.....	.....	Diet changed
10	6/14	4.31	4.04				
	6/15	4.31	4.27				
	6/16	4.31	3.31				
	6/17	4.31	3.18	5.80	—6.08	None	
	6/18	4.32	3.23				
	6/19	4.31	3.31				
	6/20	4.30	3.11				
	6/21-27	.....	....	....	.....	.....	Menstrual period omitted
11	6/28	4.31	2.75	0.27			
	6/29	4.31	3.08	1.15			
	6/30	4.31	3.04	0.65			
	7/ 1	4.31	2.61	0.82	+4.70	0.5 gm. gland	
	7/ 2	4.31	2.77	0.90			
	7/ 3	4.31	3.12	0.49			
	7/ 4	4.31	3.05	0.77			
21	10/ 6	8.04	6.76				
	10/ 7	8.00	7.88				
	10/ 8	7.67	7.26	3.21	+0.64	None	
	10/ 9	8.00	7.12				
	10/10	8.00	6.84				
	10/13-17	.....	....	....	.....	.....	Menstrual period omitted
22	10/18	8.00	6.25				
	10/19	8.04	5.91				
	10/20	8.09	6.17				
	10/21	8.00	5.66	4.81	+9.27	0.25 mg. H. I.	
	10/22	8.00	6.22				
	10/23	8.04	6.05				
	10/24	8.00	5.83				
23	11/25	8.04	5.49				
	11/26	8.00	6.00				
	11/27	8.09	6.06				
	11/28	8.00	6.50	5.30	+7.02	None	
	11/29	8.04	6.94				
	11/30	8.11	6.84				
	11/31	8.00	6.14				

considered, it is entirely possible that the thyroid hormone which, according to Kendall, contains the indol nucleus, should be split into intermediary decomposition products, one or more of which may be toxic and produce the symptoms designated as hyperthyroidism.

The symptoms of exophthalmic goiter may be divided into two groups: (1) toxic symptoms, (2) symptoms of thyroid deficiency. Group 1 contains most of the frequently occurring and striking phenomena; consequently the significance of the second group has usually remained disregarded. Group 1 includes psychic stimulation, tremor, tachycardia, lability of the sympathetic nervous system, loss of weight and nitrogen, increased basal metabolism and tendency to rise of temperature. Group 2 includes goiter, cutaneous symptoms (atrophy, pigmentation, scleroma, brittleness and loss of hair, trophic nail changes), abnormal depositions of subcutaneous fat (rare), osseous changes (imperfect ossification and epiphyseal union) fatty degeneration, especially of the heart[30] and somatic musculature, mononucleosis, metabolic disturbances similar to or identical with those in hypothyroidism — delayed glucose assimilation, creatinuria, growth disturbances in youthful cases. Certain symptoms such as weakness, loss of weight and creatinuria may properly be ascribed to either group.

With regard to the pathogenesis of this complex symptomatology, the following may be said. The toxic symptoms of exophthalmic goiter have been traced in the foregoing to the thyroid hormone itself, and are probably due to the development of toxic products produced in its metabolism. All evidence tends to indicate that the thyroid hormone is a synthetic product. It is certainly built up by the thyroid from inorganic iodin and other substances possibly related to the indol-containing amino-acid, tryptophane. It is possible that one or more of these intermediate substances is toxic, and, indeed, identical with the products arising in the breakdown of the hormone in the body. It is likewise possible that various factors might disturb the normal synthesis of the hormone, the result being the premature discharge of the toxic intermediary product into the circulation. The factors producing this condition might be disturbances in the nervous control of the thyroid metabolism, such as could be produced by fright, emotion, shock or direct organic injury such as trauma, thyroiditis, or again, histologic and gross changes in the parenchyma of the gland; that is, the well known causes of exophthalmic goiter.

The result of the premature discharge of the hypothetical toxic intermediary product would be an impoverishment of the gland of the thyroid hormone, which would explain the fact that Graves' disease goiters are poor in iodin, and especially in the active *alpha*-iodin pro-

30. Wilson, L. B.: Collected Papers of the Mayo Clinic, 1915, **7**, 438.

teins. The decreased production of the normal hormone due to the cause mentioned would tend to be accompanied or followed by the signs of thyroid insufficiency. Thus the deficiency symptoms (Group 2) can be accounted for; also the concomitant occurrence of hypothyroid and hyperthyroid symptoms, and the tendency of exophthalmic goiter patients to develop myxedema.

The frequent failure of the pathologic picture to coincide with the clinical (see the foregoing) can best be explained by these views, which do not strictly necessitate histologic change at the beginning, but rather a defective endocrine secretory metabolism as to the ultimate cause of exophthalmic goiter.

According to our hypothesis there is present in the thyroid and blood of exophthalmic goiter patients a toxic substance. This view is substantiated by the experiments of Caro,[31] confirmed by Klose by demonstrating the toxicity of the urine from exophthalmic goiter patients; also recently by Blackford and Sanford,[32] who found a depressor substance in the thyroid and serums of such patients.

Lampe, Liesgang and Klose in their voluminous monograph on Graves' Disease have developed a hypothesis somewhat similar to the foregoing. The failure of these authors to put forth an adequate explanation for the symptoms of hyperthyroidism resulting from the ingestion of normal thyroid material has, however, prevented acceptance of their views.

There remains to interpret the thyroid treatment of exophthalmic goiter with the aid of the hypothesis just advanced. The results obtained by us were (1) clinical improvement in some cases; unchanged condition in others; (2) increase in the nitrogen balance in all cases studied. The uncertainty of the effects on the clinical condition may have been due to the fact that our cases, all of which were selected before the development of the theoretical views here presented, were of the toxic type. It must be borne in mind that the introduction of normal hormone from without may not necessarily lead to a cessation of the chemopathologic processes causing the toxic symptoms of this disease. This may, indeed, prove an effectual barrier against obtaining results by thyroid, or, indeed, any medical treatment in such cases. Again, the dosage employed may not have been suitable, or the treatment sufficiently protracted. It seems insignificant, however, that the nitrogen balance improved in all cases and at times seemed to bear a relation to the amount of the thyroid hormone administered. As this same effect was also observed in hypothyroidism, but never occurred in the normal controls, it certainly suggests that thyroid defi-

31. Caro, L.: Quoted in Klose, H., Erbeb. d. inn. Med. u. Kinderh., 1913, **10,** 167.

32. Blackford, J. M., and Sanford, A. H.: Am. Jour. Med. Sc., 1913, **146,** 790.

ciency is an underlying condition in exophthalmic goiter. Our results indicate, however, that in accordance with previous experience the thyroid treatment of these toxic cases is inadvisable.

In exophthalmic goiter showing deficiency symptoms, judicious thyroid treatment would, according to our views, be indicated. Such a case has been studied with great thoroughness by Halverson, Bergeim and Hawk.[33] On 6 to 9 grains of thyroid extract daily, improvement of the clinical symptoms occurred, accompanied by a marked retention of nitrogen, calcium, magnesium, sulphur and phosphorus. Thymus had the opposite effect. It is possible that further study will demonstrate generally the value of thyroid therapy in cases of thyroid toxemia with deficiency phenomena provided they are properly selected and continuously treated.

I desire to acknowledge the excellent assistance rendered by Miss Maude Hays in the dietetic and analytical work of this research.

33. Halverson, J. O., Bergeim, O., and Hawk, P. B.: THE ARCHIVES INT. MED., 1916, **18,** 800.

THE NITRITOID CRISES AFTER ARSPHENAMIN INJECTIONS *

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HISTORICAL

Soon after the introduction of arsphenamin, in 1910, reports began to appear in the literature of untoward effects, severe reactions, and even deaths following its use intravenously. The most important papers on the subject, now grown quite voluminous, will be given in the bibliography.[1] All the different types of reactions, from simple transient fever to fatal acute hemorrhagic encephalitis or nephritis were considered. No attempt was made at first to separate out of the complexa any distinct groups or types of symptoms. As a result, much confusion and misunderstanding in the description, tabulation, interpretation and explanation of these was produced.

Gradually, one type of clinical picture occurring during or immediately after an intravenous arsphenamin injection, began to stand out. The chief symptoms were: redness of the face, dyspnea, a feeling of anguish and distress, cough and precordial pain. It was described first probably by Notthaft in 1911. In his case, collapse followed an injection of insufficiently alkalinized arsphenamin. Nevertheless he did not believe it due to the relative acidity of the solution, as he had observed a similar reaction with a prepared properly alkaline solution. In the same year, Levens published several cases of anaphylactoid symptoms after a second arsphenamin injection. Wechselmann was the first to theorize about the problem. According to him, it was caused by water contaminated by dead bacteria, molds or dissolved protein used in dissolving the arsphenamin. With freshly distilled water, he claimed, all untoward effects could be prevented. Marschalko in 1911 reported an anaphylactoid reaction after a first injection of 0.28 gm. arsphenamin, and regarded it due to molds in the water. Fischer in the same year reported a case of acute hemorrhagic encephalitis after a second injection of arsphenamin. Hoffmann and Jaffe simultaneously described anaphylactoid symptoms follow-

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* Salvarsan is the trade brand of the preparation of arsphenamin referred to in this article.

1. The references will be found in alphabetical sequence at the end of the article.

ing second arsphenamin treatments. They attempted transmission to animals, by sensitizing them with patient's serum, but they could not succeed.

In 1912 more comprehensive studies of these phenomena appeared. Iwaschenzow reported a series of 15 cases with anaphylactoid symptoms immediately after or during arsphenamin injection. He rightly emphasized their distinction from the later symptoms of acute or subacute arsenical poisoning with which Wechselmann had concerned himself or those which Ehrlich thought were caused by arsenoxid and which resemble so closely the symptoms of carbon monoxid poisoning. He concluded that the symptoms appearing immediately after or during the injection were definitely not caused by protein or organic substances in the water used, but depended on a sensitized condition of the patient which in turn varied with the dose and the interval elapsing between injections. Bruckler in the same year described nine cases. Of these, two occurred at the third injection, one at the seventh, two at the eighth, two at the ninth, and two at the tenth, in all stages, ages and varieties of syphilis.

A Frenchman, Millian, now began to publish on the subject papers presented to the *Societe francaise de dermatologie et de syphilis*. To the complex of symptoms under discussion he gave the name of nitritoid crises, because of their similiarity to those of amyl nitrite poisoning. Also, as the latter were amenable to epinephrin treatment, he applied it to the former, and obtained good prophylactic and therapeutic results.

In the same year, A. F. Swift published a paper on anaphylaxis to arsphenamin. He analyzed a series of cases; in three cases the reaction appeared at the fourth injection, in two at the fifth, in three at the sixth, and in one at the seventh. Skin hypersensitiveness was present in some of his patients. A condition of anti-anaphylaxis was apparently produced in one of his cases ten minutes after. He worked on the mechanism of the reaction. It will be considered later.

A number of other publications, to be mentioned in the bibliography, elaborating these fundamental clinical facts, but none contributing anything new to the symptomatology, or natural history, of the reaction, have appeared.

THEORIES TO EXPLAIN THE NITRITOID CRISES

With the reports of these symptoms, speculation about their meaning of course began. Wechselmann's views about the importance of contaminated water really applied only to the delayed symptoms after arsphenamin. Iwaschenzow, as said, completely exploded their value for the control of the nitritoid crisis. Attention was now paid to two

other factors: one, that of the sensitization of the patient to arsphenamin, in the anaphylactic sense; second, the acidity and concentration of the solution, and its physicochemical effect on the blood. Hoffmann and Joffe attempted to sensitize guinea-pigs to the serum of their patients, afterwards injecting arsphenamin, but obtained negative results. Auer tried to sensitize guinea-pigs directly with arsphenamin, but failed. Swift, however, using a mixture of serum and arsphenamin, was able to shock animals, getting the picture of acute anaphylaxis. Brauer, in 1912, also failed in direct sensitization of animals with the serum of patients.

As early as 1910 Willige, describing the details of a death due to arsphenamin, suggested that the concentration of the drug might be the cause of the fatality. At the same time, Hering emphasized the acidity as a factor. He varied the amount of acidity in experiments on animals. Frankel and Growen reported a death due to 0.4 gm. arsphenamin in 15 c.c. water, to which only 1.5 c.c. of normal sodium hydroxid solution was added. In 1911, Michaelis, speaking of the use of arsphenamin intravenously in acid solution, mentioned the therapeutic possibility that the drug was precipitated in the circulation by the alkalinity of the blood. That year Schottmüller claimed that acid arsphenamin added to serum in vitro produced a precipitate. Miessner reported extensive studies on animals. He found that the severity of the reaction, both in normal animals, and in those with foot-and-mouth disease, varied directly with the acidity. If the arsphenamin was alkaline, 400 mg. per kilogram could be given with impunity. On the other hand, 5 mg. per kilogram of a 0.5 per cent. acid solution caused dyspnea and often death. Necropsy showed all the organs normal except the lungs, which showed a thrombosis of the blood vessels and an inflammatory exudate in the parenchyma. He also obtained a precipitate in vitro with acid arsphenamin and serum, and thought the thrombosis due to precipitates in the pulmonary capillaries. Fleig got the same results at about the same time, but claimed the essential factor was not the hydroxyl but the phenol radical in the arsphenamin.

Three Americans now made important contributions to the problem. Auer, who had failed to produce arsphenamin anaphylaxis in animals, now demonstrated that the toxicity was inversely proportional to the acidity and concentration. This is a law that must be considered in any explanation of the nitritoid crisis. Then Don Joseph showed first that alkaline solutions, no matter if strong or weak, in large dose or small, given rapidly or slowly, produced no bad effects. Acid solutions, if highly diluted (0.6 gm. in 300 c.c.), acted likewise. If stronger, the latter caused death. A heavy pre-

cipitate was found nearly always in the right ventricle and in the lungs. Finally, MacKee proved that the weight of the precipitate in vitro varied directly as the acidity and concentration.

Two other theories should be mentioned: That of Millian is that a vasodilatation is responsible for the symptoms. This obviously begs the questions at issue. Schamberg has lately put forward the theory that the symptoms are due to the by products formed in the manufacture of arsphenamin, which he calls the substance *x*. This, like the theory of Swift, does not relate itself to the fundamental laws of the effect of acidity and concentration, or of precipitate formation, and so leaves unexplained most of the phenomena. Nor does it explain why, out of a group of persons treated with the same batch of arsphenamin, only one or two will react.

THE PROBLEM STILL TO BE SOLVED

A problem still remained. Although, as a result of the work on the importance of acidity and concentration, the use of thoroughly alkalinized arsphenamin became general, and there was a great reduction in the number of reactions, a few patients still continued to react to the most carefully alkalinized solutions injected with a technic *lege artis*. In them, it occurred generally after one injection had previously been given, and, having once happened, could be predicted to recur. The problem of the mechanism of these reactions the writer set himself to solve.

In a series of 300 consecutive arsphenamin injections eleven individuals were found who suffered from nitritoid crises when treated with properly prepared, alkalinized arsphenamin. Four of these had them on three successive occasions, and one on four. In the last case, the reaction was predicted. Saline solution, prepared as the arsphenamin solution was prepared failed to elicit the symptoms. Arsphenamin almost immediately (after the entry of 30 c.c.), produced the symptoms of the nitritoid crisis. Serum was obtained from these and from the nonreacting patients. When properly alkalinized arsphenamin was brought into contact with these serums, those from the nonreacting produced no, or a little, opalescent precipitate. Those from the eleven reacting, however, caused a heavy whitish yellow precipitate. Thus, by testing previously the serum and the solution one could say whether or not a reaction would follow the injection. In those in whom a precipitate was produced, a prophylactic dose of epinephrin seemed to prevent the onset of the nitritoid crisis. After its appearance, also, the same drug hypodermically shortened the duration of the alarming symptoms.

Having determined that the nitritoid crisis occurring with sufficiently alkaline arsphenamin in certain persons was due to intravascular precipitation (whereas previously it had been accepted that only acid salvarsan could do this), the next question that arose was, Why should the precipitate be formed only in the blood of these patients and not in that of the majority who received the same amount of drug in the same physical state? Fleig had shown that most of the precipitate produced when acid arsphenamin was added to serum consisted of protein. No determinations of the content of the blood in protein in these cases had ever been made. Blood from two patients analyzed by the nephelometric method of Kober and Graves, showed that there was an increased protein content, essentially an increased globulin content. The hypothesis may therefore be put forward, tentatively of course, in view of the small number of studied cases, that this may be the solution of the problem; that is, that the increased protein content of the blood in certain syphilitics may favor precipitation in vivo, even of properly alkalinized arsphenamin. To confirm this, of course, the blood protein of a number of syphilitics should be studied.

SUMMARY

All the data on the nitritoid crises may be explained as follows: Either because of the acidity of the injected arsphenamin or because of the increased protein, especially globulin content of the blood of certain syphilitics, intravascular precipitate formation occurs. This precipitate is responsible for the local vasodilatations, which constitute the essence of the crises. Such symptoms may be expected to follow other modes of causing intravascular precipitations. The writer has seen the symptoms of the nitritoid crisis appear after a gelatin injection given intravenously. The theories of neither Swift nor Schamberg throw light on the fundamental laws of the toxicity of arsphenamin established and confirmed by so many researches. The one fact alone that all the symptoms of the nitritoid crisis may be produced in a normal individual by a single injection of arsphenamin in an acid solution is enough to dispose of the sensitization theory of Swift. And as Iwaschenzow pointed out years ago, the fact that the same lot of arsphenamin given to a whole series of patients will produce the reaction in perhaps one or two, puts out of court any special toxic substance theory, like that recently revived by Schamberg. The other theories, without either factual or experimental support, are too numerous to mention.

To sum up: In a series of 300 arsphenamin injections, eleven patients reacted with the symptoms of the nitritoid crisis. The serum of these patients contained substances which precipitated with the

arsphenamin in vitro, and probably also in vivo, causing the symptoms by a consequent vasodilatation, controllable by epinephrin subcutaneously. The serum of two of these patients contained an increased amount of protein, especially globulin.

I wish to express my indebtedness to Dr. H. Goldenberg, attending dermatologist at the Mt. Sinai Hospital, New York, for permission to study these cases.

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A CLINICAL REPORT OF NONSPECIFIC PROTEIN THERAPY IN THE TREATMENT OF ARTHRITIS *

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Twenty-five years ago Rumpf expressed the opinion that the beneficial effects observed following the subcutaneous injections of a vaccine were the results of a nonspecific immunologic reaction. It has been only during the past five years that his contention has received serious attention from the medical profession.

In 1893, Fraenkel[1] demonstrated that he could favorably influence the clinical course of his typhoid fever patients by treating them with subcutaneous injections of killed typhoid bacilli. His associate, Rumpf,[2] went a step further and employed killed pyocyaneous bacilli instead of the typhoid bacilli. Since he obtained equally good results, he felt that he was justified in claiming that the beneficial reaction was of nonspecific character. However, Ehrlich's theory of the specificity of all immunologic reactions had such firm footing among the members of the medical profession that they refused to consider seriously the idea of a nonspecific therapy. In 1913, Victor Vaughan[3] revived interest in this question by publishing his book on the relation of protein split products to immunity and disease.

During the past three years a number of workers have contributed to our knowledge on this subject. As a result of the work of Kraus,[4] Ichikawa,[5] Ludke,[6] Saxl,[7] Novy,[8] Jobling,[9] Peterson,[10] Coley,[11] Miller

* Submitted for publication May 28, 1918.

1. Fraenkel: Ueber Spezifische Behandlung des Abdominal Typhus, Deutsch. med. Wchnschr., 1893, **19,** 958.
2. Rumpf: Die Behandlung des Typhus Abdominalis mit Abgetöteten Kulturen des Bacillus Pyocyaneous, Deutsch. med. Wchnschr., 1893, **19,** 561.
3. Vaughan, V. C.: Protein Split Products in Relation to Immunity and Disease, 1913.
4. Kraus and Mazza: Zur Frage der Vakzine Therapie des Typhus Abdominalis, München. med. Wchnschr., 1914, **61,** 1967.
5. Ichikawa: Abortive Treatment of Typhoid and Paratyphoid, Sei-i-Kwai Med. Jour., 1913, **33,** 73.
6. Ludke: Behandlung abdominal Typhus mit Intravenösen Injektionen von Albumosen, München. med. Wchnschr., 1916, **63,** 571.
7. Saxl, P.: Ueber die Einwerkung Pyrogenes Substanzen und Fieber, München. med. Wchnschr., 1916, **63,** 571.
8. Novy and de Kruif: Jour. Am. Med. Assn., 1916, **66,** 2031.

and Lusk,[12] and Culver,[13] it has become apparent that in the future this form of treatment will deserve a definite place in our list of therapeutic procedures.

Because at present this treatment is still in the experimental stage, and the clinical reports of large series of cases treated by the intravenous administration of a foreign protein are relatively few, the following report is submitted with a view to confirming its undoubted value in a large percentage of the cases. No satisfactory explanation for the beneficial results obtained by the use of this type of therapy has as yet been advanced, although numerous investigators are working on the subject at present.

We are indebted to Miller and Lusk for the suggestion of treating arthritis by intravenous injections of foreign proteins. They have reported that in their treatment of 175 cases of acute, subacute, and chronic arthritis (uncomplicated by adhesions) they obtained favorable results. Cecil[14] confirmed this opinion on a series of forty cases of acute arthritis. In this work, inasmuch as we have not attempted to restrict the type of cases to be treated, but have included practically all cases complaining of joint symptoms which have come to the City Hospital during the past six months, as well as the chronic cases, with or without adhesions, which were in the wards previous to the beginning of the treatment, we feel that we have given this method of treatment a severe test.

I am indebted to Drs. Shelby, Wightman, Quimby, Bastedo, and McCabe for the courtesy of allowing me to use the cases in both medical divisions, and to Dr. Larkin and his assistants for the dilution and administration of the vaccines.

The essential fact to keep in mind in connection with this report is that the reaction was produced as a result of the introduction of a foreign protein, or, to be more exact, a bacterial endotoxin into the blood stream. The following are a few of the different foreign proteins which have been successfully used in the treatment of arthritis: Killed typhoid,[15] gonococci,[13] colon and meningococcus bacilli and proteose.

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9. Jobling: THE ARCHIVES INT. MED., 1917, **19,** 1042.
10. Jobling and Peterson: Jour. Am. Med. Assn., 1916, **66,** 1753.
11. Coley: Treatment of Malignant Inoperable Tumors, with Toxins of Bacillus Erysipelas and Bacillus Prodigiosus. Read before Third International Conference of Cancer Research, Brussels, 1913.
12. Miller and Lusk: Jour. Am. Med. Assn., 1916, **66,** 1756.
13. Culver: Verhandl. des Deutsch. Gesellsch. f. Urol., 1913, **4,** 102. Abstr. in Jour. Am. Med. Assn., 1917, **68,** 362.
14. Cecil: THE ARCHIVES INT. MED., 1917, **20,** 951.
15. Miller, J. L.: Jour. Am. Med. Assn., 1917, **69,** 765.

In other words, one may select a bacterial, an animal, or a vegetable protein as a therapeutic agent. The clinical reaction is apparently the same following the intravenous injection of any split protein, although the required doses vary with the different proteins. In our treatment only one type of foreign protein was used, because very little is known as to the dangers of the treatment and its contraindications. It might be mentioned that although we have had not bad results, Thomas[16] declares he knows of several cases in which the treatment was followed by sudden death. With the exception of one case of hypertension, all of these patients cited by Thomas were apparently in such a serious condition at the time the vaccine was administered that they should not have been considered suitable cases for the treatment.

Typhoid vaccine from the laboratories of the board of health was used in our work. Our decision in this matter was influenced by the consideration that it would be easy to make this method of treatment accessible to the general practitioner in the future if the initial success should prove to be of permanent character. This was contrary to the advice of Miller and Lusk, who said that they were unable to obtain reliable results from stock vaccines. They used their own freshly prepared vaccines. But as the New York Board of Health laboratory products are universally accepted as standard, a thorough trial was considered advisable before condemning them. The dose of vaccine was administered in 10 c.c. of freshly prepared physiologic sodium chlorid solution.

As this type of treatment has not been extensively used, it is perhaps wise to describe in detail the effects of the most important clinical phenomena which have been observed in our series of cases.

1. *Chill.* — The injection of a foreign protein intravenously is followed after a half hour by a severe chill. It is similar in many respects to the severe chills seen in a malarial paroxysm. The entire body shakes violently. In chronic cases, these involuntary muscular contractions probably play an important part in breaking up numerous small adhesions and thus account for the increased mobility of the joints. The violence of the muscular contractions would contraindicate the use of this type of treatment during pregnancy, on account of the danger of abortion, or in the third week of typhoid, on account of the danger of perforation, or hemorrhage. The chill lasts for from twenty to thirty minutes, although occasionally the patient feels chilly for from ten to eighteen hours. During the chill, the patient should have extra blankets and hot water bottles.

16. Thomas, H. B.: Jour. Am. Med. Assn., 1917, **69**, 770.

2. *Temperature.*—A rise in temperature accompanies the chill. In moderate reactions the temperature usually goes up to 103 F. In a more severe reaction the temperature may reach 106 or 107. The patient should not be sponged or given drugs to counteract the high temperature while the general condition is good and while the pulse remains normal. As a rule, we have found that the improvement of the patient's symptoms corresponds very closely with the height of the temperature reaction. Our most striking beneficial results have been in cases in which the temperature rose to 105 and 106. Even in these cases we have never seen evidence of cardiac or respiratory distress. It is interesting to note that a number of observers have found that high temperatures artificially produced have a deleterious effect on the life and growth of the organisms of any established infections.[17] Ludke believed that the infecting organism was either killed by the high temperature, or that a more rapid and more firm union of the antigen and antibody resulted. However, since many of our joint cases are due to gonorrheal infections, the susceptibility of this particular germ to heat should be appreciated, as any marked increase in temperature destroys the life of this organism. It has been shown experimentally[18] that it is impossible to infect a patient with gonorrhea while suffering from an acute infectious disease, if the temperature at the time is 102 or over. Culver[13] quotes a case of acute urethritis of three days' duration showing typical gonococci in the smears when the patient was admitted to the hospital. On the following day, the patient had a chill, followed by a temperature of 105. Malarial parasites were found in the blood. The chills and fever were allowed to continue for four days, at the end of which time the discharge had stopped, and no gonococci could be found in the urethra or in the urine. It must be emphasized, however, that the striking therapeutic results obtained in cases of arthritis could not consistently be attributed to the beneficial effects of fever alone, as the streptococcus and other organisms generally associated with this condition are not particularly sensitive to heat.

3. *Profuse Perspiration.*—Following the chill the patient's entire body is covered by a profuse perspiration. It has a very foul odor and is strongly acid to litmus.

4. *Headache.*—This occurs in almost every case. As a rule, it is only moderate and of short duration; occasionally it is very severe, and may last as long as twenty-four hours. Miller and Lusk warn us against the use of this treatment in alcoholic patients, inasmuch as it is inclined to cause a dangerous delirium.

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17. Cited by Kyaw: Med. Klin., 1912, **8,** 1829.
18. Boerner and Santos: Med. Klin., 1904, **10,** 1062.

5. *Backache.*—In about 50 per cent. of the cases the patients complain of a severe pain in the back. This is usually bilateral, and sometimes radiates down toward the groin. In this respect it may simulate renal colic or acute renal congestion.

6. *Abdominal Pain.*—There is frequently pain in the abdomen associated with nausea and vomiting. We have noted that these symptoms almost invariably occur if the vaccines are given on a full stomach, and in cases which have not had a preliminary cathartic. Occasionally, in severe reactions, the patients have mild hematemesis. Five of our cases showed moderate gastric hemorrhages. The hemorrhage in one case persisted for a week. Although at the time the gastric hemorrhages all occurred in association with very severe reaction and high temperature, yet these patients subsequently showed the most marked clinical improvement.

7. *Pain in the Affected Joints.*—At the height of the chill, and for a few hours subsequent to it the patients almost always complain of an increase in the pain in the affected joints. This is probably due to the violent contraction and mechanical irritation produced as a result of the chill. If the pain is moderate, it can usually be controlled by small doses of acetylsalicylic acid. If the pain is severe, it is sometimes necessary to use from one eighth to one quarter grain of morphin.

8. *Blood Changes.*—1. The red cells: The red cells tested before and following the chill show no difference in their fragility. In some cases we have noted that there is a slight temporary hemolysis present following the chill. The same dose will sometimes produce slight hemolysis in one case and not in another. Hemoglobin estimations do not show any marked variation during the course of the treatment.

2. Leukocytes: Following the administration of the vaccine, there is a mild leukocytosis. Coincident with the chill, the leukocytes rapidly decrease in numbers. Usually they average 3,000 or 4,000. This in turn is followed immediately after the chill by a second leukocytosis. It usually reaches from 20,000 to 30,000, but in severe cases it may rise to 50,000 to 75,000. The increase is almost entirely due to polymorphonuclear leukocytes. At the end of twenty-four hours the leukocyte count has usually returned to normal. Jobling warns us that "We must not overemphasize the therapeutic importance of the leukocytosis, because even normal rabbits respond with a marked leukocytosis to the intravenous injection of typhoid vaccine."[19] He

19. McWilliams, Helen: Jour. Immunol., 1916, **1**, 259.

also reminds us that: "Although splendid results have been obtained by this type of treatment in typhoid fever, the normal course of recovery in typhoid is not marked by a leukocytosis."

9. *Kidney Changes.*—As a great many of these patients complain of a severe pain in the back, one naturally asks whether it can be possible that this form of treatment has injurious effects on the kidney. This phase of the subject has been particularly interesting since Longcope[20] published his article in which he claims to have produced lesions simulating those of acute and chronic nephritis in experimental animals as a result of repeated anaphylactic shocks. His contention is worthy of careful consideration and study, although it is somewhat doubtful as to whether it can be applied in cases of human nephritis. As these reactions are apparently a mild form of anaphylactic shock, it would appear, according to Longcope's theory, that we should have some evidence of renal injury in our cases of arthritis treated by this method. A number of the chronic cases have received from fifteen to forty injections, whereas most of the animals in his series were killed after having received ten injections. None of our patients has shown evidence of acute kidney injury, even after the most severe shock.

By "acute kidney injury" is meant the presence of a trace of albumin, or of macroscopic red blood cells in the urine. In the cases which had a trace of albumin and a few casts in the urine previous to the administration of the vaccine, no appreciable increase in these elements has been detected.

In a report of very careful work on this subject, presented at the meeting of the American Pathological Society in Philadelphia, April 5, 1918, Bell and Larson began by explaining that Longcope claimed to have found 15 per cent. more glomerular lesions in his animals which had been subjected to repeated anaphylactic shock than were found in the control series of apparently normal animals. Although he endeavored to exclude unsuspected or spontaneous lesions of the kidney by carefully selecting young and healthy animals for his work, he admitted having used a few animals showing mild albuminuria. In only two or three of these did he take the precaution of examining the kidney previous to the administration of anaphylactic shocks. Bell and Larson made an effort to improve on his method. They first stated that in examining different series of laboratory animals, there is a wide variation in the percentage of the cases showing glomerular lesions at necropsy. In one series of apparently healthy animals

20. Longcope: Production of Experimental Nephritis by Repeated Protein Intoxication, Jour. Exper. Med., 1913, **18,** 678.

80 per cent. showed glomerular lesions, whereas we ordinarily expect to find only about 30 per cent. showing glomerular lesions. It is not always possible to detect the presence of these lesions in the kidney, even by the most careful examination of the urine. It is therefore not safe to assume that an animal has no healed glomerular lesions on the evidence that it appears healthy and has a negative urine. They also took the extra precaution to operate in every case in order to examine the surface of the kidney for evidence of scars or small inflammatory areas previous to the administration of the foreign protein. No animal was accepted which showed either of these lesions or albuminuria. In their conclusions they say that they were unable to determine that the production of mild anaphylactic shocks in animals had a deleterious influence on the kidney. This conclusion would be in direct accord with our clinical results and with those of Culver.

10. *Blood Pressure.*—Miller and Lusk said in their paper that in their opinion a high blood pressure was a contraindication to this form of treatment. For this reason, and also as a part of the study of its effect on the kidney, the blood pressures were carefully taken in the last sixty cases included in this report. It was found that the blood pressure during the chill is usually raised fifteen to twenty points. Following the chill, it is usually lowered ten to twenty points below normal, and remains low from one to three days. In only two cases did it show a moderate rise. In one patient with a marked hypertension, the blood pressure dropped forty points. It remained low for two or three days and gradually returned to its former position. The treatment apparently had no ill effect on the condition of the patient.

11. *Heart.*—In this series, the treatment was used in ten cases of heart disease, two of mitral stenosis, three of aortic regurgitation, and five of mitral regurgitation. All of these patients were well compensated, and apparently were unaffected by the administration of the vaccine. One patient with mitral stenosis was admitted suffering from acute multiple arthritis of a very severe type. Salicylates and acetylsalicylic acid were tried for one week without affecting the temperature or improving the patient's general condition. He was given twenty million killed typhoid bacilli intravenously during the late afternoon. The following morning he was much improved. His temperature and joint symptoms, which showed a tendency to recur at irregular intervals for a period of two weeks, were easily controlled by repeating the vaccine. The patient secured a position as orderly and remained under observation for over four months without any recurrence of his symptoms. Apparently, the heart lesion remained unchanged. The other case of mitral stenosis was promptly and permanently relieved

from precordial pain by the administration of one dose of vaccine. Luthlein[21] reported a case of gonorrheal endocarditis successfully treated in this manner.

Up to the present time, no bad cardiac symptoms or signs have been observed as a result of the patients being allowed to get out of bed and walk about the wards. We have found that it is apparently unnecessary to keep the patients in bed except during the day when they receive the vaccine.

RESULTS

In reporting on the efficacy of this therapeutic procedure it is difficult to give an absolutely accurate report without going into the minute details of each case. Our report includes 110 patients treated during the past eleven months. For the sake of brevity we have grouped the cases and have attempted to give an impartial report of our clinical results.

Acute Cases.—In about 60 per cent. of the cases, one injection abruptly terminated the acute attack. A large majority of them had been unsuccessfully treated by the usual rheumatic remedies before coming to the hospital. Thirty per cent. required from one to five injections. The greater number of these obtained immediate relief from pain, although the permanency of the cure has not been established. Ten per cent. were unimproved.

Subacute Cases.—In this class we included the cases of less than one year's duration, not showing ankylosis. After repeated injections, marked improvement was obtained in 50 per cent. of these cases, considerable improvement in 25 per cent., and only slight improvement in the remaining 25 per cent.

From our observation up to date it would seem that the greatest improvement follows the first dose. It was frequently noted that intractable or obstinate cases did not improve until we had given doses sufficiently large to produce a severe reaction. Sometimes one severe reaction was sufficient; at other times it required several marked reactions to effect a definite improvement in the patient's condition.

Chronic Cases.—This class included cases which have persisted for periods lasting from one to ten years, even those with marked ankylosis. A moderate improvement in the mobility of some of the joints was noted in almost all cases. This increased mobility was particularly noted in the joints of the upper extremities. Even a small improvement is a cause for gratitude in the patient, as it allows him increased ability to use his hands and arms.

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21. Luthlein: Wien. klin. Wchnschr., 1915, **28**, 533; Jour. Am. Med. Assn., Feb. 3, 1917.

PRECAUTIONS TO BE OBSERVED

As this method of treatment is still in its infancy, a word of caution is in order. Rufus Cole advises that before the foreign protein therapeutic treatment is given to the general practitioner, experimental medicine should determine its dangers. Miller and Lusk conclude their report with the following warning: "This form of therapy is still in the experimental stage, and should not generally be applied without first a careful consideration of the dangers associated with it."

The most important dangers and contraindications which we have noted in our work up to the present time are:

1. Hemolysis may occur as a result of the intravenous use of distilled water, therefore, always dilute the stock vaccine with sterile normal salt solution.

2. Start the treatment by using small doses—five to ten millions. The average dose is considered to be about fifty millions, and the maximum dose about two hundred and fifty millions. We have frequently used much larger doses, but following these larger doses the reaction is uncertain, and sometimes dangerous. In this connection, Jobling says:

> It is almost impossible to determine beforehand the degree of reaction which will follow these intravenous injections. Some authors believe that it depends on the severity of the disease, while others consider the concentration of immune bodies in the circulating blood more important. From a general survey of the work done, however, it appears that there is some other factor as yet unknown which plays an important part in determining the severity of the reaction.

3. If a typhoid vaccine is used as a foreign protein therapeutic agent, it is necessary to remember that if only one dose has been given, the patient is sensitized to typhoid infection. To minimize danger, at least two more injections should be given—subcutaneously if necessary—in order to desensitize the patient. The second and third injections should be given within six days' interval after the first injection.

4. Before using any vaccine, inquire carefully as to the previous history of anaphylactic phenomena. Then follow up the treatment with the same type of vaccine throughout. We have had only two cases which gave mild anaphylactic symptoms. No cases of severe anaphylaxis have been reported so far in the literature, when a typhoid vaccine was used.

CONCLUSIONS

1. It has been found that intravenous injections of foreign proteins are apparently more efficacious than the usual drug treatment for the relief of cases suffering from acute, subacute, and chronic

arthritis. In making this statement, due consideration has been given to the known variation in duration of an attack of acute rheumatic fever.

2. In some cases there is a tendency to recurrence, with symptoms milder in type. A large proportion of these patients can be greatly benefited by intensive treatment. The percentage of these recurrences is no larger, if as large, as we are accustomed to see in the patients treated by drug therapy.

3. There is no evidence up to date that the foreign protein injections have an injurious effect on the kidneys.

4. Treatment is not dangerous if the foregoing precautions are observed.

5. Vaccines prepared at the Laboratory of the Board of Health give reliable and uniform results.

SEROLOGIC LOCALIZATION OF ORGANIC BRAIN LESIONS *

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During my work on dementia precox, the dialysis method of Abderhalden, slightly modified, proved to be of great value. Yet, as this method did not, for certain reasons, become very popular, I thought it imperative to show that if used properly it is quite reliable and more than that, it can be of great value in the clinical diagnosis of obscure cases.

It seemed advisable to attempt to localize by this method those gross brain lesions which could be verified either by an operation or by necropsy, or by unmistakable clinical evidence. The technic used in all experiments was a modification of the original method based on nearly 4,000 tests, was easy to perform, less complicated and perfectly reliable. The detailed description of this modification will be found in the latter part of this article.

In the cases in which the dialysis method has been used for the purpose of a focal brain diagnosis, twenty-five have been sufficiently studied clinically or verified by operation or necropsy to be considered. The clinical diagnosis or symptoms were not known to me in most of the cases of this series. The serum was delivered for examination with only the general information that the patient suffered from some brain lesion, the location of which was not even suggested, but which I was requested to locate by serologic means. After the test was made and the diagnosis from the test was noted, it was given to the clinician for final comparison.

In the general table (Table 1) summarizing the results, the portions of the brain ("substrates") taken for the single tests are named by Roman and Arabic numbers. Figures 1 and 2[1] show the gyri which correspond to the numbers in Table 1 and in the text. Table 2 represents the subcortical structures under III and IV.

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* From the Psychopathic Hospital of Cook County.

* Part of the work reported in this paper was conducted in the Otho S. A. Sprague Memorial Institute; another part in the Memorial Institute for Infectious Diseases.

1. Figures 1 and 2 are adapted from pictures in the "Human Anatomy" of Spalteholz.

TABLE 1

Case	I	II	III	IV
	1 2 3 4 5 6 7 8 9 10 12 13 14 15 16 18 19 20 22 23 24 25 27 28*	1 2 3 4 5 8 10 12 13 14 15 18† 19‡	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	1 2 3 4 5 6 7 8 9
1. Wm. V. 1/3/16	.. .. ..

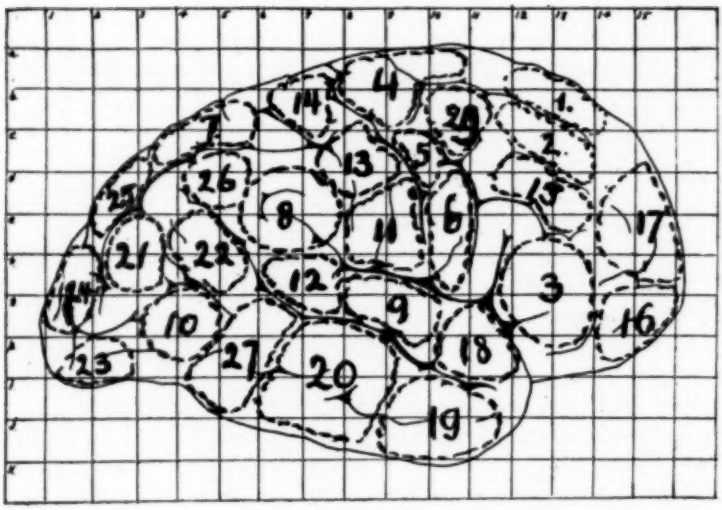

Fig. 1.—The areas of the brain cortex.

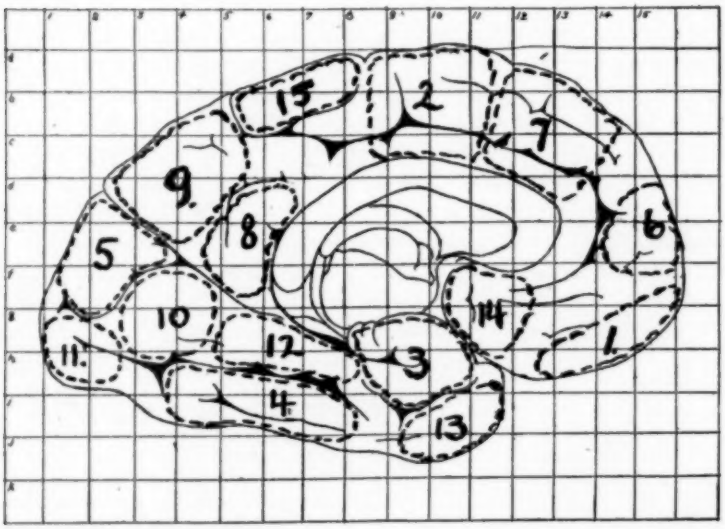

Fig. 2.—The mesial surface of the brain.

TABLE 2.—Subcortical Structures Under III and IV, Table 1

III: 1. Spinal cord, upper curvature	13. Pineal gland (human)
2. Medulla and lemniscus	14. Corpora quadrigemina
3. Pons	15. Corpus callosum
4. Corpus mammillare	IV. 1. Pineal gland (cattle)
5. Chiasma opticum	2. Pituitary (cattle, anterior)
6. Pituitary (whole, human)	3. Pituitary (cattle, posterior)
7. Olfactory tract and bulb	4. Infundibulum (cattle)
8. Fornix	5. Dura
9. Caudate nucleus	6. Cerebellar gray matter
10. Optic thalamus	7. Dentate nucleus
11. Geniculate body (lateral)	8. Internal capsule
12. Choroid plexus	9. Lentiform nucleus

APPARATUS AND TECHNIC

Dialyzers.—They are made of collodion in the following way: A 10 per cent. solution of well dried celloidin shreds in equal parts of alcohol and ether is filled into tubes ¾ by 4 inches (best with far outstanding rims; so-called fat melting point tubes). The tube is now reversed and the collodion is allowed to flow directly back into the bottle for one minute. The tube is then reversed again and allowed to stand another minute upright, until a small drop collects on the bottom of the tube. The tube is reversed again, the ring of collodion permitted to reach about the half of the height of the tube and turned back into position. Through turning of the tube the solution is now distributed evenly on the lower part of the tube. After a short experience one is able to judge just how much of the solution to let accumulate on the bottom in order to obtain a good thin tube with enough strength in the bottom to prevent folding in.

The ether vapor is blown out from the inside of the tube, which next is filled with 80 per cent. alcohol. After allowing it to stand for about twenty minutes, the alchol is poured out and the tube, with the collodion film, immersed in cool running water. After all the alcohol is washed out, which takes place after about thirty minutes, the rim is loosened, and the dialyzer can now be easily pulled out. If the dialyzer made in this way has no air bubbles and is evenly shaped, it can be used without testing. It is advisable to reject without test all those which are either uneven or too white (they ought to be just slightly milky), or if they contain in the wall, and especially on the bottom, any air bubbles. There is too much danger of breaking the very much thinner wall of air bubbles and making the dialyzer leak and consequently losing the experiment. The dialyzers are preserved in 80 per cent. alcohol and washed for half an hour in running water before every test. They can be used over and over again, only care must be taken to remove all the serum after every use. For that end it is advisable to wash them first in physiologic sodium chlorid solution to prevent any globulins from precipitating, and afterward in running water for at least one hour. They ought to be in alcohol for at least six hours between tests in order to sterilize them.

Dialyzers made in this way keep very well for many months; are ready for use at short notice, and are uniform in action.

The way of making them was adapted, with some changes, from a similar method by Pregl.[2]

Dialyzing Flasks.—Instead of the expensive Erlenmeyers with wide neck, as recommended by Abderhalden, I am using ordinary wide-mouthed, tall-form 3-ounce bottles. The advantage of these bottles is the low price, and what is more important, the possibility of utilizing a much taller column of water for dialysis, thus proportionally to the dialyzing surface increasing the rate of dialysis.

2. Pregl: Fermentforschung, 1914, **1**, 1.

Water.—Ordinary distilled water (neutral to litmus) is used.

Serum.—The blood is usually taken from any of the large veins in the arm with just enough constriction not to suppress the pulse entirely. A short needle, gage 16, was found most suitable because, while not making too big a hole in the vessel, it allows the collection of the necessary volume of blood quickly, thus preventing any annoyance to the patient. About 3 or 4 ounces of blood are collected into dry sterile bottles without the use of any anticoagulant. The blood is allowed to stand for an hour or so at room temperature, then the clot is torn to smaller pieces with sterile long hatpins and separated well from the glass, and the container left in the ice-box for several hours (over night). The serum is poured off into centrifuge tubes and centrifugated at medium speed for about ten minutes. The clear serum is pipetted off into a dry sterile graduated cylinder.

The serum should not show much hemoglobin, although that does not interfere markedly with the reaction, according to my experience. In the same way it is not essential to take blood outside of the digestive period, though it seems to give a clearer cut experiment to do so. Presence of bile in blood does not interfere with the reaction, beyond staining the dialyzers.

Substrates.—As material for my brain tissues, human brains from necropsies were used. Only brains from individuals perfectly normal, as far as the brain was concerned, were used and care was taken to use as fresh material as possible (not more than ten hours after death) to avoid postmortem changes in the tissues.

All the large vessels were removed and pieces cut out as marked in Table 2 and Figures 1 and 2. In slicing off pieces from the cortex, care was taken to remove only the gray matter, the parts from inside the fissures not being utilized at all. The pieces were cut into small particles of the size of a small pea and left stand for some time in labeled flasks filled with tap water, preferably in the ice-box. Every two hours the water was changed until all traces of blood disappeared. Now distilled water was used in the same way, and lastly distilled water with 0.5 per cent. acetic acid. After all the blood was removed from the tissue in this way, the pieces were coagulated by immersing for about two minutes in boiling water. The tissue was fished out, put back into the labeled flask and extracted cold two or three times with alcohol and as many times with ether in order to remove all fat and lipoids. When a drop of extracting fluid does not leave any fat on evaporation on a watch glass, the tissue is ready for freeing it from dialyzable substances giving the ninhydrin reaction. That is accomplished by immersing the particles in boiling water for not more than five minutes and repeating the procedure several times with fresh water. Care must be taken not to prolong the boiling too much, because then we run the danger of hydrolyzing or boiling off the specific protein. The boiling is repeated until 10 c.c. of the water in which the tissue was boiled ceases to give a reaction with 0.2 c.c. of a 1 per cent. ninhydrin solution on boiling for about three minutes; that is, until about 2 c.c. are left in the tube. The tissue is now transferred to sterile bottles, covered with boiling distilled water and about ⅛ inch of toluene. If the bottles are properly corked and the pieces, when necessary, taken out under aseptic conditions, the tissues thus prepared keep almost indefinitely. Just before the test the substrate is boiled three times, for a short while each, in distilled water.

Test Tubes.—The test tubes should not alkalinize the water on boiling and therefore only the best quality should be used—Jena, Nonsol, or best of all, Pyrex. The test tubes and the flasks are always cleaned with chromic acid.

The Test.—Into each of the dialyzing bottles 10 c.c. of neutral distilled water is measured with a pipet. The washed dialyzer is taken into the left (scrubbed) hand, a piece of the chosen substrate inserted into it carefully with a long forceps and from 0.7 to 1 c.c. of the clear serum added. The charged dialyzer, after being provided with a half inch layer of toluene over the

serum, is put into the bottle, a few drops of toluene dropped on the water and all covered with a watch glass. As many dialyzers are charged as different substrates are to be used and every bottle is labeled to avoid confusion. Besides those tissue dialyzers, an odd number (three or five) of serum control tubes (without any substrates) are rigged up in the same way. All bottles are left for twenty hours in an incubator regulated at between 26 and 30 C. This low temperature was chosen, as it is sufficient for the digestion, while it is not high enough to spoil the dialyzers by promoting in any very marked degree the hydrolysis of celloidin, which, being an ester, is hydrolyzible.

After twenty hours' incubation the water from the outside of the dialyzer is transferred into alkali-free test tubes. The contents are boiled for a short time to drive off the toluene, 2 drops of a 1 per cent. solution of ninhydrin are added and the contents of the tube again boiled briskly until only a ⅛ inch high layer is left in the test tube. If, in the case of bumping, or foaming, the liquid becomes turbid or precipitates, the test is rejected because of the possibility of the presence of protein due to a leaky dialyzer. If, on the other hand, the liquid remains clear but refuses to boil quietly, one or more short glass capillaries (sealed on the upper end) may be dropped into the tube.

The reading is made at least half an hour after the last tube is boiled, in which time the equilibrium is surely reached. The reading is made by comparison with the control tubes which sometimes are slightly colored. This may be due either to presence in the serum of digestive ferments, or amino-acids and peptones, if the blood was taken during digestion or was slightly hemolyzed. After a short experience this fact does not make any difficulties. The control tube is considered negative. Three plus was the designation given to the color which appears when 5 c.c. of a 0.1 per cent. solution of asparagin and 2 drops of the ninhydrin are added to a boiled down control tube, and the contents boiled as in all other tests. The intermediate colors are called 2 and 1 plus.

After the ninhydrin test is read the reactions are painted with colored inks —white, blue, violet, and red (3 plus)—on charts identical with Figures 1 and 2, as well as a figure indicating the subcortical structures of Table 2, but printed on transparent paper, thus showing after overimposing in transmitting light all the reactions in various levels at a time, and allowing the determination of the localization of the lesion.

RESULTS OF TESTS

Case 1.—W. V. Psychopathic Hospital, Chicago, Jan. 3, 1916. Brain tumor. Only seven different brain tissues were used as substrates. In this and the two following experiments, a mixture of all the parts of the cortex was used as substrate without differentiation. An exceedingly strong reaction with the pituitary tells the localization. Clinically, acromegaly.

Case 2.—Mr. P. Psychopathic Hospital, Chicago, Feb. 8, 1916. Brain tumor. Ten different substrates were used. The reaction with the anterior pituitary (3 plus) indicates the localization of the lesion, as would be expected, according to a clinical diagnosis of acromegaly.

Case 3.—Mr. N. Cook County Hospital, Feb. 8, 1916. Clinical Diagnosis, brain tumor. Nine different substrates were used. The cerebellar gray matter and the pons gave strong positive reactions. A necropsy performed a week later by Dr. Bissel, pathologist of Cook County Hospital, revealed a tumor in the cerebellopontine angle.

Case 4.—A. F. Presbyterian Hospital, Chicago. Dr. R. Wilder, June 8, 1916. Clinical diagnosis known to me; pineal gland disease (sexual precosity). Fourteen substrates were used. The double negative reaction with the pineal gland excludes that structure. The lesion is localized in the posterior lobe of the hypophysis (III_6 and IV_3) representing probably hypofunction, which would

produce sexual symptoms similar to those due to pineal trouble. Clinical diagnosis afterward changed to posterior pituitary insufficiency.

CASE 5.—L. D. Cook County Hospital. Dr. R. Hamill, May 18, 1916. Clinical findings, motor aphasia and right body hemiparesis. Eighteen different substrates were used. The most pronounced reactions are in the optic thalamus, pons, frontal cortex and the Broca convolution.

CASE 5a.—Same case. June 22, 1916, shows practically the same reactions, with only slight differences in intensity of positiveness.

CASE 6.—J. F. Presbyterian Hospital, Chicago. Dr. D. Lewis, June 23, 1916. Brain tumor. Fourteen different substrates used. The most important reactions are in the pituitary (III_6—3 plus) and especially its frontal lobe (IV_8—3 plus) and the occipital vision center (II_5—2 plus). Localization: The lesion is in the anterior hypophysis; visual trouble. Clinically, acromegaly; blindness.

CASE 7.—G. J. Psychopathic Hospital, Chicago, April 16, 1917. Twenty-one different tissues used as brain substrates. The reaction (3 plus) with the occipital vision center (II_5), and the anterior pituitary (IV_7—3 plus) suggest the localization of the lesion in the hypophysis. A subsequent roentgen-ray examination reveals a very small sella turcica, posterior clinoid processes much enlarged and possible pituitary hypoplasia. Clinically, visual delusions.

CASE 8.—Em. F. May 24, 1917. Twenty-one different substrates were used. Besides a 2 plus reaction in the pituitary (anterior), there is a prominent reaction with the visual center in the occipital lobe. The patient later gave a history of having suffered several years from double vision, but the relation of this to the reaction, if any, is not clear.

CASE 9.—Mr. T. Psychopathic Hospital, Chicago, Aug. 8, 1917. Clinical diagnosis, violent mania with visual hallucinations. Forty different substrates used. The motor area of the cortex shows throughout positive reactions (I_{888} and II_3), while the positive reactions with visual path represented by the cuneus (II_5—2 plus) the corpora quadrigemina (III_{16}—2 plus) and the lateral geniculate bodies (III_{13}—3 plus) correspond with the visual delusions.

CASE 10.—A. G. Dr. A. Heym, Nov. 9, 1917. Diagnosis, brain tumor. Thirty-four different substrates were used. The motor area in the cortex shows very pronounced positive reactions (I_{888}). The pituitary gives strong reactions (2 plus—III_6, IV_3). The lesion lies in the anterior lobe of the pituitary. Clinical diagnosis, acromegaly with occasional epileptiform attacks.

CASE 11.—J. M. Psychopathic Hospital, Chicago, Nov. 26, 1917. Dr. G. W. Hall. Clinical diagnosis, tumor in the left frontal lobe. Thirty-four different substrates were used. The lesion was apparently cortical, because all non-cortical tissues reacted negatively (III and IV) and lies clearly in the frontal lobe (I_{333} are 3 plus positive). Because of too small a number of different parts of the frontal cortex used for the test, no nearer localization could be attempted. The clinical findings, in short, were the following: Trauma three months previously; rapid mental deterioration for the previous month; disorientation; emotionalism; recognized objects but could not name them; general tremor; jerking of right arm at times. In the beginning of February the patient died after a second trephining (in the left frontal region) and on necropsy, performed by Dr. LeCount, was found a glioma of the left parietal lobe in the neighborhood of the base of the temporal lobe.

CASE 12.—F. A. Presbyterian Hospital, Chicago, Dec. 6, 1917. Dr. Thor Rothstein. Diagnosis, brain tumor. Fifty-nine different substrates were used. All the positive reactions in the frontal, central, parietal and occipital lobes could be centered by the association tracts in the temporal lobe and especially in its basal part. Here, too, were the two most pronounced reactions (I_8 and II_4). Pathology in that region would very well explain the reaction with the corpora quadrigemina (III_{14}) and the cerebellar gray matter (IV_6). It seems

that the lesion was located in the base of the temporal lobe in its white matter and that the pressure was directed mostly toward the adjoining parts of the cerebellum and possibly the corpora quadrigemina.

The clinical findings related to me after finishing the test were the following: Pupils large and equal; right does not respond to light or accommodation; left sluggishly; vision in right practically absent; distinct temporal hemianopsia in the left; no evidence of involvement of cranial nerves; rigid neck; passive motion in all directions causes pain, which is also the cause of difficulty in rising from recumbent position; vomiting; fainting spells; all reflexes normal; spinal pressure 265. Clinical diagnosis, tumor of the hypophysis. Since the patient left the hospital without being operated on, neither the clinical nor the serologic diagnosis could be confirmed.

Case 13.—S. S. Cook County Hospital, Jan. 28, 1918. Dr. G. W. Hall. Diagnosis, probably brain tumor. Fifty-nine different substrates were used. The lesion was evidently cortical, since all the most pronounced reactions appeared in the convex surface ($I_{2\ 3\ 6\ 13\ 25}$—3 plus). All of these areas could be centralized through the association fibers in I_3. Hence the localization of the lesion in the upper part of the third frontal convolution. Clinically, tumor in the right frontal lobe.

Case 14.—Stan. G. Cook County Hospital, Jan. 28, 1918. Dr. Hamill. Aphasia and right body hemiplegia. Fifty-seven different substrates were used. The 3 plus reaction with the Broca convolution suggested aphasia. Three plus reactions with the lower anterior central convolution is accounted for, on one hand, by the strong reaction with the internal capsule (2 plus—IV_8), on the other hand, by an apparent degeneration of fibers connecting the motor area with the base of the caput nuclei caudati (3 plus—III_6) and running thence through the corpus subthalamicum and the lemniscus (III_7—1 plus).

Thus the lesion, of whatever nature it is, must lie in the lower portion of the anterior central gyrus and Broca's convolution, causing aphasia, right body hemiplegia, and probably involvement of the fifth, seventh, and twelfth cranial nerves which originate in said area.

Case 15.—V. B. Cook County Hospital, Feb. 11, 1918. Dr. Hamill. Aphasia. Sixty-one different substrates were used. The reaction shows diffuse changes following pretty closely the areas supplied by the middle cerebral artery and especially its external striate branch, so that only a hemorrhage or thrombosis can be suggested without any centralized localization. Clinical diagnosis, thrombosis involving the Broca convolution.

Case 16.—T. K. Aug. 31, 1917. Cook County Hospital. The following clinical diagnosis was given to me subsequent to the completion of the test: Sudden blindness from secondary optic atrophy; probable cause, serous meningitis.

The test was performed with forty different substrates. The strongest reaction (3 plus) was with the cuneus and corpora quadrigemina, 2 plus with the optic chiasm. In short, the test was strongly positive with the visual fibers of the brain, and indicated that some pathologic process involved these fibers. This entirely corresponded with the clinical symptoms as already stated.

Case 17.—C. D. Sept. 24, 1917. Cook County Hospital. Dr. G. W. Hall. Clinical diagnosis, possible brain abscess or cerebral thrombosis.

The reactions, which were made with thirty-six different substrates, were, when positive, located almost only in the cortex and apparently scattered. The frontal lobe (I_1-I_2-I_3—see Fig. 1) proved to be strongly positive, though the corpus callosum, corpus mammillare, and the medulla reacted slightly positively. The path of the association indicated that the posterior part of the second frontal convolution was the probable seat of the lesion (point between I_2-I_{4-5}).

The necropsy performed by Dr. John Nuzum, pathologist of the Cook County Hospital, revealed a solitary abscess in exactly this place.

Case 18.—H. S. Oct. 3, 1917. Presbyterian Hospital, Chicago. Dr. P. Bassoe. Clinical diagnosis, brain tumor. The reaction was tested with forty different substrates and indicated in the first place that the lesion was not in the cortex. The most pronounced reactions were with the cerebellar gray matter (IV_6), with the dentate nucleus (IV_7), anterior pituitary and the corpus callosum. The final diagnosis from the test was: lesion in the cerebellum, which was found at the operation in the form of a large cyst of the upper frontal part of the cerebellum.

Case 19.—M. O'B. Presbyterian Hospital, Chicago. Dr. James B. Herrick. Clinical diagnosis, brain tumor. Forty substrates were used. The strongest reactions were with the posterior pituitary, with the chiasm the lateral geniculate bodies (III_{11}), the cuneus (II_5), the olfactory bulb (III_7) and the uncus (II_8).

The strong positive reaction with the optic chiasm explains the *2* plus with the vision center in the occipital lobe; especially because the reaction with the lateral geniculate body was 3 plus, thus completing the number of positive reactions throughout the central visual path. The *2* plus reaction with the olfactory apparatus, due probably to pressure from the pituitary, suggests an olfactory disturbance, a fact which would explain the *2* plus reaction with the olfactory sensory area (II_3). This suggestion is still more upheld by the *2* plus reaction with the corpus mammillare (III_4), which, as known, holds some relation to the sense of smell. The reaction with the thalamus (III_{10}) probably can be explained as involvement secondary to that of the corpus mammillare, possibly through the fasciculus thalamo-mammillare (bundle of Vicq d'Azyr). The *2* plus reaction with the choroid plexus would indicate intracranial pressure. Thus the localization of the lesion in the posterior pituitary.

After delivery of the complete report the following clinical and laboratory details were given: Diagnosis of tumor in the hypophysis; roentgen-ray examination shows great destruction in the sella turcica. Ophthalmologic examination: Visual field of left side destroyed almost completely; in the right eye very much subnormal. Almost complete loss of smell on the left side as compared with the right side.

Case *20*.—Mrs. H. Oct. 18, 1917. Presbyterian Hospital, Chicago. Dr. P. Bassoe. Clinical diagnosis, brain tumor. Forty different substrates were used. The most pronounced reactions were in the fornix (III_1), the optic chiasm (III_2) and the anterior pituitary (IV_2); *2* plus reactions in the optic thalamus (III_{10}) and the choroid plexus (III_{12}), a weak reaction with the caudate nucleus (III_9), the other part of the hypophysis (IV_3), the olfactory apparatus (III_7) and the corpus callosum (III_{13}).

Since there was a general diagnosis of tumor, an attempt was made to localize it in one of the enumerated structures. A lesion in the pituitary or in the chiasm causing such strong reaction would undoubtedly cause visual disturbances and reflect on the geniculate bodies, corpora quadrigemina and the visual center in the sensory area of the occipital lobe; since these parts gave negative reactions the localization was to be in the fornix or the thalamus, and it was decided that it was most likely in the fornix, because a lesion in the thalamus probably would have brought about secondarily some cortical reactions which are missing.

After delivery of my report and localization I was informed that clinically there was no localized lesion, but an internal hydrocephalus of the third ventrical with pressure directed mostly toward its frontal wall. The reactions obtained in the test, as can be seen, are in no way contradictory to that diagnosis. Only the posterior wall of the third ventricle—the corpora quadrigemina and the pineal body—are represented by a negative reaction, while all its frontal, superior and lateral structures gave strong reactions that indicate their involvement possibly from pressure. Some time after this test the patient had a left temporal decompression performed, and since then developed signs indicating tumor in the right hemisphere.

CASE 21.—M. K. Cook County Hospital, Oct. 23, 1917. Service of Dr. J. Grinker. Clinical diagnosis, tumor or abscess of the cerebellopontine angle. This clinical diagnosis was known to me when this test was made.

Thirty-eight different tissues were used. The five weak reactions in the cortex (Table 1) are in apparently no direct relation to each other and exclude the idea of a cortical lesion, but the strong reaction (3 plus) with corpus callosum (III_{18}) suggests that those reactions are bilateral. The basal ganglia, with the sole exception of the pineal gland, were negative. Thus the remaining positively reacting structure—the pons (III_5)—must be the seat of the lesion, while the 3 plus with the choroid plexus (III_{12}) indicates probably increased intracranial pressure which led to the clinical diagnosis of brain tumor. The clinical localization in the cerebellopontine angle was based chiefly on the involvement of cranial nerves from III and XII. The necropsy performed on Nov. 10, 1917, by Dr. J. Nuzum, showed pressure on the pons by a large tumor from the nasopharynx.

CASE 22.—Mrs. G. Oct. 22, 1917. Michael Reese Hospital, Chicago. Dr. S. Kuh. Clinical diagnosis, brain tumor. Thirty-eight different substrates used. The whole aspect of the reaction points to two areas of possible lesion—the frontal lobe and the corpora quadrigemina. If we consider the lesion in the frontal convolution, then it would be expected that the corpora quadrigemina would be involved too, through the degeneration of corresponding association fibers, while if the primary lesion were to be in the corpora quadrigemina the reaction with the chiasm (III_3) would naturally have to be stronger than found. In addition, the prevalence of strong reactions alone points to the localization of the lesion being in the frontal lobe; probably the posterior part of the second frontal convolution.

After receiving this serologic localization, Dr. Kuh disclosed his clinical findings, which led him to the localization of the tumor in the second frontal convolution.

CASE 23.—H. G. Oct. 23, 1917. Cook County Hospital. Dr. G. W. Hall. Clinical diagnosis, brain tumor. The number of positive reactions in the subcortical regions suggested the making of an attempt to localize the tumor outside of the hemispheres. On account of that, the fibers running from all cortex areas showing positive reactions were traced. The first thing which attracts the attention is the involvement of the cortical origin of the central path of cranial nerves III and XII (with the exception of the accessorius), the cortical origin of nerves V and XII is located in the lower two-thirds of the anterior central gyrus and is here represented by positive reactions (I_5 and I_6), while the oculomotor and trochlear originate in the superior portion of the second frontal convolution which gave a 3 plus reaction (I_2). The nuclei of all these nerves give a positive reaction (III_2) and it is to be remembered that the nuclei of the third and fourth cranial nerves lie nearest to the walls of the fourth ventricle and that they derive from a cortex area giving a 3 plus reaction; the corpora quadrigemina are 2 plus positive, and the centrifugal fibers from the temporal (I_9) and occipital lobe (I_{10}) run through the posterior commissure, the nearest structure to the corpora quadrigemina; the choroid plexus (III_{12}), the cerebellar gray matter (IV_6) and the dentate nucleus (IV_7) all gave a very distinct positive reaction.

On the basis of this analysis the lesion was localized in the fourth ventricle, with the involvement of the dentate nucleus and the gray matter of the cerebellum, of the aqueduct of Sylvius and of the corpora quadrigemina as far as the pineal gland. A possibility of a second focus in the hypophysis was pointed out (IV_{28}).

The clinical diagnosis was (as disclosed after the tests were reported) tumor in the region of the lower temporal lobe of the right side, with pressure involving the corpora quadrigemina.

The necropsy performed Oct. 26, 1917, by Dr. J. Nuzum revealed a large soft glioma beginning in the dentate nucleus, and extending over the corpora quadrigemina. The hypophysis was undermined by a cyst.

Case 24.—Mr. X. Nov. 9, 1917. Private patient of Dr. B. G. Hassin. Diagnosis, well localized brain lesion. The result of the test (Table 1) made with thirty-six different substrates did not admit of any other diagnosis than that of a lesion in the upper motor area ($I_{1\,2\,4}$). The clinical diagnosis, received as usual after the delivery of the serologic report, was: Jacksonian epilepsy confined to the left leg only, due to an old skull trauma.

Case 25.—Mr. XX. Nov. 16, 1917. Private patient of Dr. A. Heym. Diagnosis, epilepsy possibly due to a localized lesion. Thirty-seven different substrates used. The test shows besides rather weak reactions in the parietal and temporal lobes a very strong reaction (3 plus) over the whole extent of the anterior central convolution (I_{4-6}) and the paracentral gyrus (II_2).

The strong positive reactions with the caudate nucleus and corpus mammillare (3 plus—III_5, IV_4) are explained by the fact that the fasciculus subcallosus, which originates in the anterior central convolution, is interrupted in the caudate nucleus, while the central cortical path of the tegmentum, which originates in the same cortical area, after crossing the caudate and lentiform nuclei passes into the neighborhood of the corpus mammillare.

On the basis of the serologic findings the lesion was localized in the upper part of the central convolution. An operation performed ten days later revealed a deep tumor of the size of a hazelnut, which could be easily palpated in this location.

In this brief report the discussion of the individual cases has been purposely omitted and only the most important and striking features have been noted. On the basis of the findings in the limited series, the serologic diagnosis is supported in four cases by the post mortem findings, in two cases by an operation, and in fifteen cases the serologic findings are in complete agreement with definite clinical evidence. Two cases differ from the clinical diagnosis, but the diagnosis has not been controlled by necropsy or operation. In one case (Case 11) the necropsy findings proved that the serologic diagnosis was erroneous.

THE TREATMENT OF GENERAL PARESIS*

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The first question to be decided in describing the treatment of general paresis is that of the diagnosis. In this clinic we subdivide neurosyphilis into two main types, the mesoblastic and the parenchymatous; thus making the anatomic lesion coincide more or less with the clinical picture.

The mesoblastic type of neurosyphilis is again subdivided into the endarteritic, the meningitic, and the gummatous forms. Since it is not our intention to describe the treatment of these particular forms, we content ourselves with merely mentioning them.

Parenchymatous syphilis of the central nervous system is differentiated, first, according to the location of the lesion, and secondly, according to the clinical picture. Thus, we distinguish between tabes and general paresis, and can further speak of a diffuse cerebral, a focal cerebral, a cerebellar and a tabetic type of the latter disease. We can also speak of a simple dementing type, an expansive type, a type with depressive symptoms in the foreground, etc.

This is quite clear whenever we deal with outspoken clinical pictures, but in incipient paresis, diagnosed mainly by the laboratory findings, the great question arises: When shall we consider a patient having a positive Wassermann in the blood and spinal fluid, a paretic gold curve, a high cell count and positive globulin tests, as a case of general paresis? All this involves fine anatomic differentiation, and, what is more, a coupling of this differentiation with the serologic findings. With the present state of our knowledge we are unable to say, with any degree of accuracy, when a possibly vague cerebrospinal involvement becomes clearly parenchymatous, and whether this corresponds to the time when the serologic tests become the same as those of outspoken general paresis.

For the purpose of this report we will class as paretics all those patients who have the serologic findings of the disease and show any mental symptoms whatever. We feel that we are justified in doing this, for it has been our experience that there is not a single psychotic

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manifestation which cannot be simulated by general paresis. Thus, we have seen a patient in what was at first glance an acute catatonic condition, who had neither neurologic nor physical findings characteristic of general paresis, but who nevertheless showed positive serologic tests. That this patient, William Brown,[1] a summary of whose case appears toward the end of our report, was really a paretic, was proved by subsequent developments. Again, we have frequently seen incipient cases whose complaints are mostly neurasthenic and hypochondriacal. We believe that too much stress cannot be placed on these subjective feelings and wish to emphasize the necessity of observing minor and apparently unimportant neurologic conditions, as well as the necessity of looking for the socalled "fraying of the personality," in such instances. The condition of a patient may not present anything strikingly abnormal to the examiner, yet when carefully interrogated, the relatives or friends may furnish conclusive proof of a gradual decrease of the patient's efficiency and a diminution of his initiative.

Three of the cases reported are essentially tabes with primary optic atrophy. The patients had practically no mental symptoms, except depressions reactive to the realization of their condition.

Syphilitic optic atrophy, an atrophy of the nerve-head, itself a continuation of the cerebral parenchyma, would seem so closely allied to a degeneration of this parenchyma that we feel we are not going too far afield in including such cases in our series. We realize that the blindness tends to localize and neutralize the progressive degenerative factors. We have taken into account this empirically well-known clinical fact, in deciding whether or not the patient was improved.

At this juncture we should like to describe our laboratory technic briefly. Cell count, Pandy and Ross-Jones tests, are too well known to merit restatement. The Wassermann was run with the usual technic, using the antigens described by one of us.[2] The colloidal gold solution was standardized according to the technic of Miller, Brush, Hammers and Felton.[3] We might remark that we agree with Felton[4] in believing this test to be the result of a quantitative interrelation of the globulin and albumin of the spinal fluid. Not a single spinal fluid giving a paretic curve was observed among the two thousand fluids examined thus far, which gave negative globulin tests. We have been able to produce solutions of globulin manufactured from paretic as well as "luetic zone" and meningitic spinal fluids. All such solutions give typical paretic curves.

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1. All names are fictitious, and are chosen to indicate race or descent.
2. Neymann and Gager: Jour. Immunol., 1917, **2**, 573.
3. Miller, Brush, Hammers and Felton: Bull. Johns Hopkins Hosp., 1915, **26**, 391.
4. Felton: Tr. Am. Med. Assn., 1917, p. 73.

Not an inconsiderable number of the paretic patients examined show negative blood Wassermann reactions, namely, twenty-nine out of a total of 126, or 23 per cent. A few of these were afterwards controlled by the Hecht-Weinberg-Gradwohl modification[5] and about 50 per cent. were positive. It is therefore evident that the widespread idea of a necessarily positive blood Wassermann in general paresis is a chimera.

We will now describe twenty-four cases treated by various methods, partly on account of special exigencies of the individual cases, partly because we wished to draw our own conclusions as to the best form of therapy. (Tables 1 to 10; summarized and classified as to results of treatment in Table 11.)

At present the following forms of therapy are used:

The long-established mercury treatment combined with potassium iodid may be discarded as used alone. It is, however, recommended by practically all clinicians as a valuable aid to the other forms of therapy.

Next to this in simplicity is the intravenous treatment. This may sometimes produce results, as is best shown in the case of Mary Olafson, Table 1. We gave this patient, whose weight was but 102 pounds, fifteen intravenous treatments, a total of 7.3 gm. in eight weeks. We thought we had found a simple and adequate way of influencing the serologic findings in the spinal fluid. These ideas were dispelled when we applied the same method to another patient, Leonard Benson, Table 2, an incipient case, who showed fraying of the personality and who reacted to intraspinous salvarsanized serum,[6] with perineal parasthesias, and to biweekly injections of the diarsenol brand of arsphenamin with an acute arsenical neuritis, in addition to a slight arsenical rash. Perhaps the use of this preparation, which we have come to view as a more toxic preparation than the arsenobenzol brand of arsphenamin or the salvarsan brand, was at fault; more likely, however, the patient was a victim of hypertherapy. We believe that intravenous arsphenamin or its substitutes may help certain cases, but that the danger point is too near the optimum therapeutic.

The resistance of the choroid plexus and the meningeal blood vessels to the passage of arsphenamin and other chemical compounds of complex molecular structure has been demonstrated by McIntosh and Fildes[7] and others. One must take these organs by storm, so to speak, before one can hope to reach the *Spirochaete pallidae* buried in the depths of the cortex.

5. Gradwohl: Jour. Am. Med. Assn., 1917, **68,** 514.

6. Serum obtained after intravenous treatment with arsphenamin or any of its substitutes is denoted as arsphenaminized serum.

7. McIntosh and Fildes: Brain, 1916, **39,** 478.

Intraspinous therapy with arsphenamized serum is undoubtedly useful, but we believe that the same objections apply to it as to the intravenous treatment, unless one wishes to use the usual Swift-Ellis procedure[8] and the modification of Ogilvie,[9] alternately once a week. If arsphenamized serum is given every seven days in the manner described, great care must be taken to avoid bladder, rectal and other root disturbances. We have seen serious disturbances of this nature in no less than six of our patients. In three, the symptoms were transitory and the patients finally recovered complete control of their muscles; with three the results were exceedingly regrettable, in that one developed a permanent and almost complete paraplegia, while the other two remained incontinent. This factor is not to be lightly gone over and is a danger that is always present. A patient may react well to five or six treatments and show subjective or objective bladder disturbances with the seventh. J. W. Brooks, Table 3, the above mentioned paraplegic, amply illustrates this phase. The serologic improvement is apparent, and coincides with the arrest of deterioration. Were it not for the root disturbances the disease would probably have been arrested after further treatment. We have observed such more or less permanent motor root disturbances, as well as perineal and sacral anesthesias and parasthesias, after intraspinous mercurialized serum.

The reactions which one gets with mercurialized serum, prepared according to the Byrnes method[10] are entirely different. Here the immediate reactions are much more severe, yet, as stated, we have never seen a permanent injury to the muscular or sensory innervation. We believe, however, that little can be accomplished tending toward arresting the disease and changing the serologic findings by the use of this method alone. John Hogan, Table 4, who received thirteen intraspinous mercurialized serum injections, totalling over one third of a grain of mercuric chlorid, will best illustrate this point. Deterioration and death were not prevented. The serologic tests were not influenced. Here we gave the maximum doses of one twenty-fifth of a grain. We do not consider this high dosage as the most efficacious one for general use. The reactions with most patients are far too severe. There really is an enormous amount of irritation, causing high temperatures, extreme pain, meningismus, nausea, etc. We feel that a maximum amount of intensive treatment should and must be given, yet that this must not interfere to such an extent with the patient's general health that it will lower his resistance.

The intraventricular treatment of Hammond and Sharpe[11] and the

8. Swift and Ellis: New York Med. Jour., 1912, **96,** 53.
9. Ogilvie: Am. Jour. Syphilis, 1917, **1,** 509.
10. Byrnes Jour. Am. Med. Assn., 1914, **63,** 2162.
11. Hammond and Sharpe: Jour. Am. Med. Assn., 1915, **65,** 2147.

TABLE 1.—Record of Treatments

Mary Olafson; aged 22. Ward E2, E1. Admitted Jan. 14, 1917. Discharged March 8, 1917

Date	Intravenous Arsphenamin	Intraspinous S. Serum, C.c.	Intraspinous M. Serum	Blood Wassermann Antigen			C. Spinal Fluid Wassermann Antigen									Cells per C.mm.	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			B			C				Ross-Jones	Pandy			
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
1/16	...	....	.....	4*	4	4	4	...	...	4	...	...	4	...	...	93	+	+	5555554320		
1/18	0.3	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	Sl.	
1/21	0.5	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
1/25	0.4	....	.....	3	4	0	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
1/28	0.5	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
1/31	0.5	....	.....	4	4	4	4	...	...	4	...	...	4	...	...	39	.....	.....	.....	0	Bloody fluid
2/ 4	0.5	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
2/ 7	0.5	....	.....	4	4	4	4	...	...	4	...	...	4	...	...	13	(+)	+	5555552000	0	
2/12	0.5	....	.....	4	4	3	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	Sl.	
2/15	0.5	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	++	
2/20	0.5	....	.....	2	1	1	4	...	...	4	...	...	4	...	...	10	(+)	(+)	5444320000	0	
2/24	0.5	....	.....	0	1	0	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
2/27	0.5	....	.....	0	1	1	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	Sl.	
3/ 7	0.6	....	.....	0	1	1	2	...	...	2	4	4	3	...	...	....	.....	.....	.....	+	Bloody fluid
3/15	0.5	....	.....	0	0	0	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
3/19	0.5	....	.....	0	0	0	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	Sl.	
3/27	...	....	.....	...	...	...	2	...	..	4	4	4	4	...	...	N. C.	(+)	+	4433331000		

* In this and the following tables 4 means 100 per cent. fixation; 3 means 75 per cent. fixation; 2 means 50 per cent. fixation, etc.

TABLE 2.—Record of Treatments

Leonard Benson; aged 51. Ward W3. Admitted Dec. 13, 1916. Discharged April 16, 1917

Date	Intravenous Arsphenamin	Intraspinous S. Serum, C.c.	Intraspinous M. Serum	Blood Wassermann Antigen			C. Spinal Fluid Wassermann Antigen									Cells per C.mm.	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			B			C				Ross-Jones	Pandy			
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
12/15	...	....	.....	4	4	4															
12/20	0.2	....	.....	...	...	...	4	...	...	4	...	...	4	...	...	70	++	+++	5555544210	0	
12/28	0.5	24	.....	4	4	4	4	...	...	4	...	...	4	...	...	78	+++	+++	5555543321	0	
1/ 4	0.6	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	Tonsillitis
1/15	0.6	....	.....	...	...	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	Sl.	
1/18	0.6	22	.....	4	4	4	4	...	...	4	...	...	4	...	...	22	++	+++	5555543210	0	
1/25	0.6	15	.....	4	4	4	4	...	...	4	...	...	4	...	...	7	++	+++	4555555531	0	
2/ 1	0.6	24	.....	4	4	4	4	...	...	4	...	...	4	...	...	17	+++	+++	5555553300	0	
2/ 8	0.6	24	.....	4	4	4	4	...	...	4	...	...	4	...	...	19	++	+++	5555554320	+	
2/15	0.6	23	.....	4	4	4	4	...	...	4	...	...	4	...	...	14	++	+++	5555443100	+	
2/20	0.6	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	Incontinence
2/23	0.5	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
2/27	0.6	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	+	
3/ 3	0.6	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
3/ 7	0.6	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
3/10	0.5	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
3/14	0.6	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	+	Slight arsenic rash, arsenical neuritis
3/23	...	....	.....	...	...	...	4	...	...	4	...	...	4	...	...	8	+	++	5555542100		

TABLE 3.—Record of Treatments

J. W. Brooks; aged 50. Ward W2, W1. Admitted Aug. 16, 1916. Discharged Nov. 2, 1917

Date	Intravenous Arsphenamin	Intraspinous S. Serum, C.c.	Intraspinous M. Serum	Blood Wassermann Antigen			C. Spinal Fluid Wassermann Antigen									Cells per C.mm.	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			B			C				Ross-Jones	Pandy			
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
8/22	...	....	.....	0	1	0	4	...	...	4	...	...	4	...	...	51	++	+++	5555543210		
8/24	0.2	....	.....	...	...	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	SI	
8/30	...	....	1/100	...	...	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	+	
9/ 9	0.6	25	.....	0	0	0	4	...	...	4	...	...	4	...	...	....	.....	.....	.....	+	Bloody fluid
9/15	...	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	....	.....	.....	.....	+	Bloody fluid
9/21	0.6	21	.....	0	1	0	4	...	...	4	...	...	4	...	...	58	+++	+++	5555555321	+	
9/29	...	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	31	+++	+++	5555554200	+	
10/ 5	0.6	22	.....	0	0	0	4	...	...	4	...	...	3	...	...	20	++	++	5555555310	0	
10/12	...	....	1/100	...	...	...	4	...	...	4	...	...	4	...	...	15	++	++	5555555420	SI.	
10/19	0.6	22	.....	0	0	0	4	...	...	4	...	...	4	...	...	19	++	+++	4554432100	0	
10/26	...	....	1/50	0	0	0	4	...	...	4	...	...	4	...	...	17	++	+++	3444444310	+	
11/ 1	0.6	27	.....	0	0	0	4	...	...	4	...	...	4	...	...	15	+++	+++	4553222000	0	
11/ 9	0.6	35	.....	0	0	0	4	...	...	4	...	...	4	...	...	11	++	+	4444321000	++++!	Gradually developing incontinence and paraplegia
12/ 5	...	....	.....	...	...	...	2	...	...	4	...	...	2	...	...	11					
9/ 3	...	....	.....	0	1	0	1	...	...	4	...	...	1	...	...	10	.....	.....	2224442200		

TABLE 4.—Record of Treatments

John Hogan; aged 51. Ward W 3, 2, 1. Admitted Dec. 19, 1916. Discharged June 11, 1917

Date	Intravenous Arsphenamin	Intraspinous S. Serum, C.c.	Intraspinous M. Serum	Blood Wassermann Antigen			C. Spinal Fluid Wassermann Antigen									Cells per C.mm.	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			B			C				Ross-Jones	Pandy			
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
12/22	.....	....	.....	4	4	4	4	...	...	4	...	...	4	...	...	64	+	++	5555543210		
12/28	0.2	....	.....	4	4	4															
1/18	. ...	....	1/400	...	...	...	4	...	...	4	...	...	4	...	...	.....	.....	.....	.....	0	Bloody fluid
1/25	.....	....	1/100	...	...	...	4	...	...	4	...	...	4	...	...	29	+++	+++	5555555531	0	
1/31	.....	....	1/75	...	...	...	4	...	..	4	...	...	4	...	...	38	+++	+++	5555554431	Sl.	
2/ 7	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	30	+	++	5555555500	++	
2/15	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	24	+++	+++	5555554320	Sl.	
2/20	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	21	+++	+++	5555555420	Sl.	
3/ 1	.....	....	1/37	...	...	...	4	...	...	4	...	...	4	...	...	24	+	++	5555554310	Sl.	
3/ 7	0.3	....	1/37	4	4	4	4	...	...	4	...	...	4	...	...	....	.....	.....	.....	Sl.	Bloody fluid
3/15	.....	....	1/25	...	...	...	4	...	..	4	...	...	4	...	...	14	+++	+++	4555555321	Sl.	
3/22	.....	....	1/25	...	...	...	4	...	...	4	...	...	4	...	...	48	+++	+++	5555544100	Sl.	
3/29	.....	....	1/25	...	...	...	4	...	...	4	...	...	4	...	...	31	++	+++	5555555421	Sl.	
4/ 5	.....	....	1/25	...	...	...	4	...	...	4	...	...	4	...	...	....	.....	.....	.....	Sl.	Bloody fluid
4/12	0.5	....	1/25	2	4	2	4	...	..	4	...	...	4	...	...	26	++	++	5555554210	Sl.	Patient steadily deteriorated
6/11	.....	....	.....	4	4	3	4	...	...	4	...	...	4	...	...	....	.....	.....	.....	...	Died in a state hospital 2 months later

TABLE 5.—Record of Treatments

Wilhelm Sturdivant; aged 36. Ward W 2, 3. Admitted May 31, 1916. Discharged Oct. 23, 1916

Date	Intravenous Arsphenamin	Intraspinous S. Serum, C.c.	Intraspinous M. Serum	Blood Wassermann Antigen			C. Spinal Fluid Wassermann Antigen									Cells per C.mm.	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			B			C				Ross-Jones	Pandy			
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
6/ 2	.....	....	.....	4	4	4	4	...	...	4	...	...	4	...	...	6	++	++	5555553320		
6/ 3	0.4	....	.....	...	...	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
6/ 8	0.6	10	.....	4	4	4	4	...	...	4	...	...	4	...	...	6	+++	+++	5555555210	0	
6/14	.....	....	1/100	...	...	...	4	...	...	4	...	...	4	...	...	10	+	+++	5555553211	Sl.	
6/22	0.6	15	.....	4	4	4	4	...	...	4	...	...	4	...	...	7	++	++	5555542000	0	
6/30	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	10	+	+++	5554321000	Sl.	
7/ 6	0.6	25	.....	4	4	4	4	...	...	4	...	...	4	...	...	38	+	+++	5544331100	0	
7/13	0.6	28	.....	4	4	4	4	...	...	4	...	...	4	...	...	....	.....	.....	.....	Sl.	Bloody fluid
7/19	0.6	23	.....	4	4	4	4	...	...	4	...	...	4	...	...	63	+	++	5544431000	0	
7/27	0.6	25	.....	4	4	4	4	...	...	4	...	...	4	...	...	7	+	++	4555543210	++	
8/ 3	0.6	16	.....	4	4	4	4	...	...	4	...	...	4	...	...	8	+	++	4545543100	0	
8/10	0.5	21	.....	4	4	4	4	...	...	4	...	...	4	...	...	3	+	++	4444431000	0	
8/17	0.5	20	.....	4	4	4	4	...	...	4	...	...	4	...	...	2	+	++	5554432110	0	
8/24	0.6	10	.....	...	...	...	4	...	...	4	...	...	4	...	...	N. C.	+	++	4443322100	0	
8/30	.....	....	1/50	...	...	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
9/ 9	0.6	10	.....	3	4	4	4	...	...	4	...	...	4	...	...	N. C.	+	+	4444443100	0	
9/15	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	18	+	++	5544443210	0	
9/21	0.6	18	.....	4	4	4	4	...	...	4	...	...	3	...	...	....	.....	.....	.....	+	Bloody fluid
9/29	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	5	+	+	5555531000	++	
10/ 5	0.6	22	.....	4	4	4	4	...	...	4	...	...	4	...	...	10	+	++	5555554321	0	
10/12	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	7	++	++	5555555500	Sl.	
10/19	0.6	10	.....	4	4	4	4	...	...	2	...	...	3	...	...	7	+	++	2333321000	0	Discharged
12/ 5	.....	....	.....	4	4	4	4	...	...	4	...	...	4	...	...	5	(+)	(+)	2222553300	...	Second admission, Jan. 6, 1917
1/11	0.3	25	.....	4	4	4	1	...	...	2	4	4	0	...	...	3	(+)	+	1112222000	0	
1/18	.....	....	1/50	...	...	...	0	...	...	3	...	...	0	...	...	4	(+)	+	2224542000	+	
1/25	.....	....	1/50	...	...	...	0	...	...	1	4	4	0	...	...	14	(+)	+	1244544100	Sl.	
2/ 1	0.3	....	.....	4	4	4	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
2/ 2	.....	....	1/50	...	...	...	1	...	...	3	4	4	0	...	...	2	(+)	(+)	2222221000	+	
2/ 8	.....	....	1/50	...	...	...	...	...	...	...	...	...	...	...	...	11	+	+	2333443300	+	Anticomplementary
2/15	0.2	....	.....	4	4	4	0	...	...	0	3	4	0	...	...	4	+	++	2231110000	0	
2/20	.....	....	1/50	...	...	...	1	...	...	1	4	4	0	...	...	3	0	(+)	1445553210	Sl.	Discharged Feb. 23, 1917. Ambulant treatments follow
3/ 3	0.3	22	.....	4	4	3	0	...	...	0	0	4	0	...	...	N. C.	(+)	(+)	1112210000	0	
3/10	0.5	20	.....	3	4	3	0	...	...	0	4	4	0	...	...	12	+	+	1113331000	0	
3/17	0.6	....	.....	3	4	3	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	Slight incontinence. Attempted suicide April 25, 1917. Removed to sanitarium
5/25	.....	....	.....	4	4	4	0	...	...	1	3	4	0	...	...	N. C.	+	+	2222200000		
9/21	.....	....	.....	1	1	0	1	...	...	0	1	3	0	...	...	5	0	0	1123332000		
1918 1/22	.....	....	.....	2	2	1	0	...	...	0	1	1	0	...	...	2	(+)	(+)	1123310000	...	Patient no longer shows bladder disturbances

TABLE 6.—Record of Treatments

William Brown; aged 29. Ward W 1, 2, 3. Admitted March 21, 1916. Discharged Aug. 1, 1916

Date	Intravenous Arsphenamin	Intraspinous S. Serum, C.c.	Intraspinous M. Serum	Blood Wassermann Antigen			C. Spinal Fluid Wassermann Antigen									Cells per C.mm.	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			B			C				Ross-Jones	Pandy			
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
3/28	.....	....	.....	4	4	4	4	...	...	4	...	...	4	...	...	72	+	+	5555530000		
3/30	0.4	....	.....	...	...	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
4/14	0.6	15	.....	...	...	...	4	...	...	4	...	...	4	...	...	32	+++	+++	5555582100	0	
4/21	.....	....	1/50	4	4	4	4	...	...	4	...	...	4	...	...	....	.....	.....	.....	Sl.	Bloody fluid
5/ 1	0.6	25	.....	4	4	4	4	...	...	4	...	...	4	..	...	22	+	+	5555554320	0	
5/10	0.6	20	.....	...	...	...	4	...	...	4	...	...	4	...	...	7	++	+++	5555542100	0	
5/17	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	42	+++	+++	5555443330	Sl.	
5/22	0.6	....	.....	2	2	2	4	...	...	4	...	...	4	...	...	10	+	+	5554443100	0	
6/ 1	0.6	10	.....	0	2	1	4	...	...	4	...	...	4	...	...	9	+++	+++	5555553310	+	
6/ 8	0.6	20	.....	0	1	0	4	...	...	4	...	...	4	...	...	18	++	+++	5555553110	Sl.	
6/14	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	6	+	++	5555554321	+	
6/22	0.6	16	.....	0	4	3	4	...	...	4	...	...	4	...	...	11	+	++	5555500000	0	
6/29	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	17	+	+++	5555422210	0	
7/ 6	0.6	17	.....	2	4	3	4	...	...	4	...	...	4	...	...	6	+	+++	5555543210	0	
7/13	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	18	+	++	5555542110	Sl.	
7/20	0.6	24	.....	2	4	3	4	...	...	4	...	...	4	...	...	10	++	+++	5555543100	0	
7/27	0.6	24	.....	4	4	3	4	...	...	4	...	...	4	...	...	6	++	+++	5555543310	0	Discharged
9/12	.....	....	.....	1	4	1															
9/21	0.6	16	.....	3	4	3	1	...	...	4	...	...	3	...	...	10	+	+	.....	...	Second admission, Sept. 20, 1916
9/29	.....	....	1/50	...	...	...	3	...	...	4	...	...	3	...	...	1	++	++	5555542100	+	
10/ 5	0.6	20	.....	2	2	1	4	...	...	4	...	...	4	...	...	14	++	++	5555554300	++	
10/12	.....	....	1/50	...	...	...	4	...	...	4	...	...	3	...	...	20	+	+	5555555320	0	
10/19	0.6	30	.....	0	0	0	4	...	...	4	...	...	4	...	...	7	+	+	5555555420	Sl.	
10/26	.....	....	1/50	...	...	...	2	...	...	0	...	4	0	...	...	21	++	+++	2454433220	Sl.	
11/16	0.5	7	.....	0	1	0	3	...	...	4	...	...	0	...	...	9	+	+++	1113333300	+	Discharged Oct. 31; Readmitted Nov. 12, 1916
11/23	0.6	30	.....	0	0	0	1	...	...	3	...	...	0	...	...	1	++	+	2333310000	0	
1917							0	...	...	2	4	...	0	...	...	5	+	+	2223333200	+	Discharged Nov. 26, 1916. Ambulant treatments follow
1/ 9	.....	....	.....	0	1	0															
1/23	.....	....	.....	...	...	...	0	...	...	1	4	4	0	...	...	4					
2/ 2	.....	....	.....	0	1	1	0	...	...	0	2	4	0	...	...	3	(+)	(+)	3334452210		
2/ 5	0.6	....	.....	0	0	0	...	...	...	...	...	...	...	...	...	....	0	0	2223331000		
4/ 9	0.6	....	.....	0	0	0	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	+	
4/23	0.6	....	.....	2	2	1	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
5/ 1	.....	....	.....	...	...	...	1	...	...	2	4	4	1	...	...	4	.....	.....	.....	+	
5/ 7	0.6	....	.....	1	3	0	...	...	...	...	...	...	...	...	...	....	+	+	4222100000		
5/28	0.6	....	.....	0	1	1	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
7/23	0.4	....	.....	0	0	0	0	...	...	0	0	0	0	...	...	2	.....	.....	.....	0	
10/ 9	.....	....	.....	0	1	0	0	...	...	0	0	0	0	...	...	2	(+)	(+)	3333710000	0	
1918																	(+)	(+)	2223100000	0	
1/15	.....	....	.....	0	0	0															
1/22	.....	....	.....	...	...	...	0	...	...	0	1	1	0	...	...	2	(+)	(+)	2223221000	0	

TABLE 7.—Record of Treatments

Isaac Goldberg; aged 42. Ward W 1, 2. Admitted May 26, 1916. Discharged Aug. 29, 1916

Date	Intravenous Arsphenamin	Intraspinous S. Serum, C.c.	Intraspinous M. Serum	Blood Wassermann Antigen			C. Spinal Fluid Wassermann Antigen									Cells per C.mm.	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			B			C				Ross-Jones	Pandy			
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
5/30	.....	....	.....	4	4	4	4	...	...	4	...	...	4	...	...	....	.....	.....	.....	...	Bloody fluid
6/ 1	0.3	....	.....	...	...	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
6/ 8	0.6	20	.....	0	3	2	4	...	...	4	...	...	4	...	...	8	+	++	5544420000	Sl.	
6/14	.....	....	1/100	...	...	...	4	...	...	4	...	...	4	...	...	7	+	+	5555443210	Sl.	
6/22	0.6	8	.....	4	4	4	4	...	...	4	...	...	4	...	...	8	++	++	5555542210	0	
6/30	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	11	+	+++	5554311000	Sl.	
7/ 6	.....	....	1/50	...	...	...	4	...	...	4	...	...	4	...	...	21	+	+++	5544321000	Sl.	
7/13	0.6	25	.....	0	1	0	4	...	...	4	...	...	4	...	...	24	+	+++	5554432100	0	
7/20	0.6	27	.....	4	4	4	4	...	...	4	...	...	4	...	...	23	+	++	5544321000	Sl.	
7/27	0.6	24	.....	3	3	3	4	...	...	4	...	...	4	...	...	18	+	++	2224541110	Sl.	
8/ 3	0.6	14	.....	2	3	2	4	...	...	4	...	...	4	...	...	....	.....	.....	.....	0	Bloody fluid
8/10	0.5	27	.....	1	4	3	4	...	...	4	...	...	1	...	...	N. C.	+	++	2233331000	0	
8/17	0.5	20	.....	0	1	0	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
8/24	0.6	20	.....	0	2	0	4	...	...	4	...	...	4	...	...	N. C.	+	++	3444321000	0	Discharged; second admission Jan. 17, 1917
1/18	0.6	20	.....	0	0	0	0	...	...	0	2	4	0	...	...	8	(+)	(+)	2234432210	++	
1/25	.....	....	1/50	...	...	...	0	...	...	0	3	4	0	...	...	15	(+)	(+)	1224443200	Sl.	
2/ 1	0.6	23	.....	0	0	0	0	...	...	0	2	4	0	...	...	14	(+)	+	2222330000	+	
2/ 8	0.6	16	.....	0	0	0	0	...	...	0	4	4	0	...	...	14	0	(+)	2223332200	0	
2/15	0.6	....	.....	0	0	0	0	...	...	0	0	1	0	...	...	6	+	+	1112222100	0	Discharged Feb. 17, 1917
2/24	0.5	....	.....	0	0	0	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
10/12	.....	....	.....	0	0	0															

TABLE 8.—Record of Treatments

James Kelly; aged 45. Ward W3. Admitted Sept. 2, 1915. Discharged Oct. 22, 1915

Date	Intravenous Arsphenamin	Intraspinous S. Serum, C.c.	Intraspinous M. Serum	Blood Wassermann Antigen			C. Spinal Fluid Wassermann Antigen									Cells per C.mm.	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			B			C				Ross-Jones	Pandy			
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
9/ 3	.....	....	.....	0	0	0	4	...	...	3	...	...	2	...	...	8	+	+	5554432100		
9/ 8	0.5	....	.....	...	...	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
9/13	0.6	20	.....	...	...	...	3	...	...	4	...	...	2	...	...	10	+	+	3444421000	0	
9/22	0.6	10	.....	...	...	...	...	...	...	...	...	...	...	...	...	11	+	+	4444332100	0	Anticomplementary
9/29	0.6	10	.....	0	0	0	0	...	...	0	...	...	0	...	...	4	+	+	4443311100	0	
10/ 6	0.6	30	.....	...	...	...	0	2	...	0	...	...	0	...	...	8	+	+	2222221000	0	
10/13	0.6	20	.....	...	...	...	0	0	...	0	...	...	0	...	...	9	(+)	(+)	2222222210	0	
10/20	0.6	30	.....	0	0	0	0	4	...	0	3	...	0	4	...	3	(+)	(+)	.....	0	

TABLE 9.—Record of Treatments

Mabel Andrews; aged 42. Ward E 3, 4. Admitted April 3, 1916. Discharged May 27, 1916

Date	Intravenous Arsphenamin	Intraspinous S. Serum, C.c.	Intraspinous M. Serum	Blood Wassermann Antigen			C. Spinal Fluid Wassermann Antigen									Cells per C.mm.	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			B			C				Ross-Jones	Pandy			
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
4/ 7	.....	....	.....	4	4	4	0	...	...	2	4	...	0	...	...	21	+	++	4555532100		
4/14	0.6	15	.....	...	...	...	4	...	...	4	...	...	4	...	...	11	+	+	3444321000	Sl.	
4/21	.....	....	1/50	...	...	...	0	...	...	0	4	...	0	...	...	....	.....	.....	.....	Sl.	Bloody fluid
5/ 1	0.6	25	.....	4	4	4	2	...	...	3	4	4	2	...	...	14	+	+	2233331000	++	
5/10	0.4	18	.....	...	...	...	0	...	...	0	0	4	0	...	...	8	+	+	1123331100	Sl.	
5/17	.....	....	1/50	...	...	...	0	...	...	0	0	0	0	...	...	8	+	+	2222332100	+	Discharged. Second admission June 21, 1916
5/22	0.5	21	.....	4	4	4	4	...	...	0	4	4	4	...	...	3	0	(+)	3333321000	Sl.	
6/30	.....	....	1/50	...	...	...	0	...	...	0	3	3	0	...	...	5	(+)	++	1112211000	Sl.	
7/ 6	0.6	25	.....	4	4	4	3	...	...	3	4	4	3	...	...	7	(+)	+	1112210000	Sl.	
7/13	.....	....	1/50	...	...	...	0	...	..	0	3	4	0	...	...	6	0	(+)	2222222100	Sl.	
7/20	0.6	31	.....	3	4	4	0	...	...	1	4	4	1	...	...	12	(+)	(+)	1222210000	Sl.	
7/27	0.6	24	.....	4	4	4	0	...	...	0	4	4	0	...	...	4	(+)	+	1112342100	Sl.	Discharged July 31. Readmitted Aug. 3, 1916
8/ 3	0.6	....	.....	4	4	4															Discharged Aug. 9, 1916. Final report submitted from another clinic
1917 10/22	.....	....	.....	3	3	3	0	...	...	0	...	...	0	...	...	4	0	0	0000000000		

TABLE 10.—Record of Treatments

Mary Hitzel; aged 35. Ward E 2. Admitted April 27, 1917. Discharged July 26, 1917

Date	Intra venous Arsphenamin	Intra spinous S. Serum C.c	Intra-spinous M. Serum	Blood Wassermann Antigen			C. Spinal Fluid Wassermann Antigen									Cells per C.mm.	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			B			C				Ross-Jones	Pandy			
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
1/23	.....	....	.....	...	...	...	0	...	...	2	4	4	0	...	..	17	+	+	5555555420	...	Dispensary reports
2/ 2	0.3	....	.....	...	2	.	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
2/ 9	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	... ..	.....	0	
2/16	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
2/23	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
3/ 2	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
3/ 9	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
3/16	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
3/23	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
3/28	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
3/30	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
4/ 3	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
4/10	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
4/13	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	
4/17	0.3	....	.....	...	0	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	0	Admitted April 27, 1917
5/ 1	.....	....	.....	1	4	1															
5/ 2	0.6	....	.....	1	4	2	0	...	...	C	4	4	0	...	...	5	+	++	5555441000	Sl.	
5/ 9	0.6	....	.....	1	3	0	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	Sl.	
5/16	0.5	....	.....	1	1	.1	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	Sl.	
5/18	.....	22	.....	...	...	...	0	...	...	0	0	...	0	...	...	5	+	+	5555542100	Sl.	
5/23	.....	....	1/200	...	...	...	...	...	...	...	...	...	...	...	...	....	.....	.....	.....	Sl	Anticomplementary; bloody fluid
5/30	0.6	....	.....	1	2	0	0	...	...	0	0	2	0	...	...	6	++	++	5555553100	Sl.	
6/ 8	....	....	1/50	...	...	...	0	...	...	0	3	4	0	...	...	5	+	+	5555542100	++	
6/15	0.6	18	.....	..	..	...	0	..	.	0	0	3	0	..	...	....	.....	.....	.....	Sl.	Bloody fluid
6/23	....	....	1/50	.	..	..	0	..	..	0	0	4	0	..	...	8	+	+	4555552222	0	
6/29	0.6	22	....	1	4	0	0	.	.	1	2	4	0	...	...	5	+	++	5555542200	+	
7/16	3.3	...	1/50	0	0	0	0	..	.	0	1	3	0	..	...	6	+	+	5555541000	Sl.	
7/23	0.4	25	...	0	0	0	0	..	.	0	0	0	0	..	...	10	++	++	4555531000	Sl.	

TABLE 11.—Data and Classification of Authors' Cases

PROBABLY ARRESTED

No.	Name	Diagnosis	Present Clinical Status and Occupation	Serologic Tests after Treatment	Duration of Present State
1	Wilhelm Sturdivant	General paresis, cerebral type	Well, but in a sanitarium	Practically negative	12 months
2	William Brown	General paresis, cerebral type	Well; butcher	Practically negative	15 months
3	Isaac Goldberg	General paresis, cerebral type	Well; tailor	Practically negative	14 months
4	James Kelly	General paresis, focal type	Well; bookmaker	Practically negative	27 months
5	Mabel Andrews	Cerebrospinal lues	Well; household duties	Practically negative	17 months
6	Mary Hitzel	General paresis, focal type	Well; household duties	Negative, except atypical gold curve	6 months

IMPROVED

7	Mary Olafson	Cerebrospinal lues; probably general paresis	Whereabouts unknown	Improved	?
8	Tina Burroughs	General paresis, cerebral type	At home	Unchanged	Being treated
9	Richard Smith	Taboparesis	Undergoing further treatment	Unchanged	Being treated
10	Charles Green	Taboparesis and primary optic atrophy	At work; clerk	Unchanged	7 months
11	Samuel Rich	Taboparesis and primary optic atrophy	At work; actor	Unchanged	7 months
12	Carl Listerman	Tabes with 8th nerve involvement	At home; works	Improved	9 months

UNIMPROVED

13	John Hogan	General paresis, cerebral type	Died	Unchanged	
14	Harry Blumenstein	General paresis, cerebral type	At work; clerk	Unchanged	
15	Fred O'Shay	General paresis, cerebral type	In state hospital	Unchanged	
16	Thomas Black	Taboparesis and primary optic atrophy	At home; in charge of nurse	Unchanged	
17	Frank O'Neil	General paresis, cerebral type	Died	Unchanged	
18	Thomas Sutton	General paresis, focal type	At home; in care of family	Unchanged	

HARMED

19	J. W. Brooks	General paresis, cerebral type	Paraplegia; in state hospital	Slightly improved	
20	Ralph Fisher	General paresis, cerebral type	Died, July 4, 1917	Unchanged	
21	Sidney McIntosh	General paresis, cerebral type	Incontinent; in state hospital	Unchanged	
22	Leonard Benson	General paresis, cerebral type	At home; arsenic neuritis	Unchanged	
23	Albert Haupt	Taboparesis and primary optic atrophy	Died; acute arsenic poisoning	Improved	
24	John Suderman	General paresis, cerebral type	Died in a convulsion six days after a treatment	Unchanged	

intradural Cotton[12] methods are undoubtedly very praiseworthy. The flow of the spinal fluid, as has been shown by Weed,[13] is toward the foramen of Magendie, starting from the ventricles and from the spinal canal. A therapy embracing these anatomic-physiologic considerations is therefore the most rational. Yet our patients, fairly early cases, dread the necessary surgical procedures, besides we agree with Cotton[12] who says: "Given an early case of paresis we would say that the Swift-Ellis method was as efficient as any." We furthermore believe that early cases are the only ones which can be arrested, and that even could a more advanced case be arrested, the result achieved would be regettable from the social aspect. We have arrested one such case, Wilhelm Sturdivant (Table 5). The history follows:

CASE 1.—Wilhelm Sturdivant, aged 36; accountant; admitted May 31, 1916.

Date of Infection.—Chancre 1902, without secondaries; sporadic treatment; mercury by mouth.

Life History.—Excellent educational opportunities; married in 1908; happy marriage; two children; no miscarriages; efficient in business.

Onset of Psychosis.—Marked irritability in spring of 1912, easily provoked; homicidal episode. There was no marked change until 1915, when he became rather inefficient and had to give up his work and loafed around; trip to Europe on account of nervousness; no improvement. January, 1916, he attempted to work in a bank but had to give up the position in March, 1916, on account of eye trouble and general inefficiency. An examination disclosed a left Argyll Robertson pupil. At this time he was sent to a state hospital, where he remained until his admission to this Clinic, May 31, 1916.

Status on Admission.—Rather agreeable; euphoric in regard to his illness; lack of judgment; was prone to hold long-winded pointless conversations; slurring speech; left Argyll Robertson pupil; right pupil sluggish; marked ataxia; tremor of tongue; knee and ankle jerks absent on both sides; anesthesia of both legs below the level of iliac crests; for serologic findings, see Table 5.

Diagnosis.—Taboparesis (moderately advanced).

Progress During Treatment.—Showed no signs of irritability; sent home on Oct. 23, 1916, where he remained in about the same condition, but had a tendency to meddle in household affairs. Readmitted for further treatment Jan. 6, 1917. Speech had markedly improved; general attitude had remained the same. Sent home again Feb. 23, 1917. Ambulatory treatment was given until March 17, 1917; then treatment was stopped because the spinal fluid became almost negative and the patient developed slight bladder symptoms. The patient tried to hold several positions, but was discharged for his inefficiency. April 25, 1917, he attempted suicide by gashing his throat with a razor, because he realized that he would not be able to hold a position commensurate with his social standing. He was sent to a private institution, where he has done fairly efficient work under guidance. No more bladder disturbances. His mental condition remained stationary up to the time of this report.

Thus we see a rather advanced, arrested case, in which the patient is now a burden to himself and family.

Wilhelm Sturdivant was not treated according to what later became our routine procedure; that is, once a week with either intravenous

12. Cotton: Am. Jour. Insan., 1915 and 1916, **72**, 125, 355 and 485.
13. Weed: Jour. Med. Research, 1914, **31**, 21, 51 and 93.

arsphenamin and intraspinous arsphenamized serum, or with mercurialized serum. The details of this routine are given below:

After the diagnosis is established, the patient is put on a routine course of mercurial inunctions and potassium iodid by mouth. Careful attention is paid to mouth hygiene during the entire period of treatment. We give these inunctions six days a week and a hot bath on the seventh day, and give a saturated solution of potassium iodid, beginning with 15 drops three times a day, and increasing one drop a day until the maximum of 150 drops a day is reached. Usually furunculosis is noticed before this time, thereupon the iodid is discontinued for about a week, to be later recommenced at 15 drops three times a day.

Arsphenamin is given intravenously, beginning with 0.2 or 0.3 gm., according to the body weight of the patient. If the patient reacts badly to this initial dose, all treatment is discontinued and we make no further attempt to treat him. We consider as serious reactions any signs of arsenical rash, neuritis, albuminuria, and marked circulatory disturbances; that is, syncopal attacks..

The next week the patient is given 0.5 or 0.6 gm. of arsphenamin. At the completion of the arsphenamin administration, 50 c.c. of blood are withdrawn into a sterile centrifuge tube, a lumbar puncture is made and the spinal canal is drained.

We are indebted to Dr. Henry A. Cotton for this suggestion, believing, as he and Barbat[14] do, that this procedure partly overcomes the aforementioned resistance of the choroid plexus and meningeal vessels to the drug. It is marvelous how much fluid one can withdraw from the spinal canal of a paretic without causing the slightest discomfort; in fact, the more fluid withdrawn, the less reaction is likely to result. We have withdrawn as much as 80 c.c. at one time.

The next day the blood, which has been allowed to clot in the ice box over night, is centrifuged, poured into a second sterile centrifuge tube, again centrifuged and inactivated in a water bath, at 56 C. for half an hour. This overcomes the use of pipets, which, even when plugged with cotton, always involve the danger of salivary contamination.

The third week $\frac{1}{100}$ grain of mercury (Mulford's mercurialized serum) is given intraspinally. Though we know by the work of Besredka[15] that animals can be sensitized to foreign protein by intraspinal injections, we have not found that this particular preparation causes reactions which might be interpreted as anaphylactic.

The fourth week, arsphenamin and arsphenamized serum are again given as described.

14. Barbat: Jour. Am. Med. Assn., 1918, **70,** 147.
15. Besredka: Compt. rend. Soc. de biol., 1910, **68,** 1110.

The fifth week, 1/50 grain of mercury is introduced in the spinal canal, provided the patient has theretofore shown no unfavorable reaction after the initial dose.

From now on the alternate treatment with arsphenamin and intraspinal mercury proceeds regularly. This is no dogmatic rule. Each patient presents his individual problem and must be treated as a human being, not as a member of a group of cases.

We have arrived at this particular form of treatment from practical as well as theoretical considerations. If we hope to accomplish results, and by results we mean clinical and serologic recoveries, we must use all the antisyphilitics at our disposal, being careful not to overdo the therapy as before stated.

Whenever a patient begins to evince signs of debility, it is best to give him a complete rest and discontinue all treatment. Whenever possible and practicable, we send such patients home. After such a rest we were often surprised to find that patients who had shown no improvement during extensive and intensive treatment, suddenly became serologically negative of their own accord. This "recuperation phase" is well shown by William Brown, Table 6. His history follows:

Case 2.—William Brown, aged 29; butcher; admitted March 21, 1916.

Date of Infection.—Possibly December, 1914; no history of secondaries; sporadic and unreliable treatment.

Life History.—Passed third grade of public school; married November, 1915, a girl who was three months pregnant by him; unhappy marriage on account of religious difficulties; fairly efficient as a butcher and delivery man.

Onset of Psychosis.—December, 1915, the patient was found wandering aimlessly on the street at 3 a. m.; could not tell what he was doing and only cried; sat around at home for some time, but later, February, 1916, began to work. March 14, 1916, he refused to eat or talk, stood in one corner of the room for six hours, and wandered aimlessly around the house saying, "I had sixty dollars. Where are they at?" He remained in this condition, eating nothing and speaking only a few words, until his admission to this clinic on March 21, 1916.

Status on Admission.—The patient lay quietly in bed, eyes open; seemed to notice people who came into the room but would answer no questions. He had to be tube-fed and catheterized; neurologic and physical status negative except for sluggish oval pupils. Tentative diagnosis, catatonic reaction type. For serologic findings, see Table 6.

Diagnosis.—General paresis, cerebral type (early stage).

Progress During Treatment.—Tube-fed until March 24, 1916. Then the patient gradually became more and more responsive, treatments having begun March 30, 1916. More or less indifference was manifested until about the middle of April, 1916. From this time on he was normal. He was discharged Aug. 1, 1916. Readmitted for further treatment Sept. 20, 1916. Serologic findings showed *first improvement.* Discharged Oct. 31, 1916. Readmitted Nov. 12, 1916. Discharged Nov. 26, 1916. Went to work at his old job. Treated sporadically and ambulantly until July 23, 1917. Continued to work during this time. At the time of this report he was earning as much money as before his illness and his mental and physical status was quite normal. His pupils were round, regular and reacted promptly to light and accommodation.

Reverting to our twenty-four cases and tabulating them (Table 11), we can divide these patients into four main groups according to the results achieved. Each of these groups embraces six patients, or 25 per cent. of the total number.

The patients of the first group are all doing well and all except one, Wilhelm Sturdivant, whose history has already been given, have been discharged from the hospital and are at work. The serologic findings of the spinal fluids of five of them are practically negative, except for slightly positive globulin tests and consequently a slight atypical change in color in the tubes of higher dilution of the colloidal gold. One of them still shows strongly positive globulin tests and consequently an atypical paretic gold curve. The blood Wassermann of two has not become completely negative.

We have found that it is possible to change the serologic findings of most patients who are given the intensive treatment outlined above. Of course this change is not always permanent. It is easiest to reduce the number of cells per cubic millimeter. We have always observed a reduction of the cell count after repeated spinal punctures and thorough drainage of the spinal canal. Consequently, a reduction of the cell count alone, unless at least a month has elapsed since the last puncture, is unimportant. The Wassermann reaction can only be reduced to negative in the spinal fluid after long intensive treatment. It is hopeless to expect a change until at least eight intraspinous treatments have been given. Often there is no change until after the fifteenth or twentieth injection. Therefore, a patient who has not had at least eight intraspinous treatments, at weekly intervals, can be said to have been *inadequately treated*. In successfully treated cases, traces of the luetic amboceptor usually remain, when double and quadruple the quantity of spinal fluid is used without increasing the other biologic reagents; that is, complement, antigen, hemolytic amboceptor and sheep corpuscles. The colloidal gold curve is often changed; in so far that the first tube may show a more or less reddish tinge, similar to the color observed in typical meningitic curves. We do not consider this a true change or improvement, since we have often seen it in patients who have again shown typical paretic curves after a respite from treatment. It is probably due to meningitic irritation, a consequence of the therapy. A true change in the gold curve, such as is shown in five of the six cases of Group 1 (Table 11), can only be obtained after a maximum number of intraspinous treatments. Even then it is not usual for the gold curve to revert to a completely negative reaction. All this is in close conjunction with the positive or slightly positive globulin findings, which are encountered in practically all cases of cerebrospinal lues after treatment. Such a trace of globulin may perhaps be regarded as

an irritation phenomenon, due to permanent changes in the injured parenchyma and mesoblast.

We have already given the clinical histories and serologic charts of Wilhelm Sturdivant and William Brown. We will now present those of the remaining four patients in the first group.

Case 3.—Isaac Goldberg, aged 43; tailor; admitted May 26, 1916. (Table 7.)

Date of Infection.—Unknown.

Life History.—Poorly educated; married in 1898; happy marriage; one miscarriage; six children living; two dead; efficient at his work.

Onset of Psychosis.—August, 1915, he began to be overtalkative and became forgetful. He was unable to do efficient work; talked about making a lot of money and the possibility of becoming governor of the state; piled the household garbage in heaps on the kitchen floor; attempted suicide by turning on the gas.

Status on Admission.—Variable swings of mood, but on the whole, placid and euphoric; easily upset by trifles, but soon laughed them away; no insight; speech and writing intact; neurologic status normal; for serologic findings see Table 7.

Diagnosis.—General paresis, cerebral type (early stage).

Progress During Treatment.—Remained in about the same state, with gradually decreasing euphoria and a gradual development of insight. Discharged Aug. 29, 1916. Readmitted for further treatment Jan. 17, 1917. Complained of headache, and had been unable to hold various jobs. Seemed clinically normal. Discharged Feb. 17, 1917. Went to work and from this time on did exceedingly well; earned more money than he had previously, because he learned to do cutting. He had only one ambulant intravenous treatment, since he felt well and was afraid of the pain during and after treatment.

This is a treated patient who is back at work and who is not only socially possible, but actually helps support his large family.

Case 4.—James Kelly, aged 45; bookmaker and gambler; admitted Sept. 2, 1915. (Table 8.)

Date of Infection.—Chancre in 1888; no treatment; no secondaries.

Life History.—Moderate education; free and easy life as a gambler and racetrack follower; abnormally free sex life; occasional sprees. Married in 1913; happy marriage; no children.

Onset of Psychosis.—The patient had an epileptiform convulsion in July, 1913, and was unconscious for about twenty minutes. July, 1914, had another similar attack. Jan. 22, 1915, he had a third attack and began taking iodids. July 14, 1915, he had a fourth attack and had an anterograde amnesia for events for a period of two weeks.

Status on Admission.—Perfectly clear mentally; good grasp on the situation; no memory defect; no speech or writing defect; neurologic status normal; for serologic findings, see Table 8.

Diagnosis.—General paresis; cerebral type.

Progress During Treatment.—Continued normal and had no further convulsions; was back at his old work and doing well Dec. 1, 1916. He has since been reported as still at work.

Case 5.—Mabel Andrews, aged 42; admitted April 3, 1916. (Table 9.)

Date of Infection.—Unknown.

Life History.—Excellent education; married in 1904; happy marriage; no miscarriages; efficient in her household duties.

Onset of Psychosis.—In 1913 the patient had a condition described by the husband as "blind staggers." No headache but marked dizziness and "saw

double." The attacks lasted a few seconds over a period of two to three weeks. At the beginning of February, 1916, the patient became overanxious about an invalid sister. Feb. 19, 1916, she became dizzy; said her "head felt funny" and that she "was going crazy"; wept and asked incessant questions about trivial matters. There was an amnesia for these few days of confusion.

Status on Admission.—Overtalkative and euphoric; memory for dates very poor; retention good; calculation and general information poor; marked lack of personal cleanliness; insight good; speech and writing unimpaired; pupils regular; right pupil markedly sluggish to light; left less so; right knee-kick practically absent; left unimpaired; no sensory changes. For serologic findings, see Table 9.

Diagnosis.—Cerebrospinal lues; probably beginning parenchymatous process.

Progress During Treatment.—The patient gradually became querulous and depressed; showed marked and unfounded dislike for certain persons. Discharged May 29, 1916. Readmitted June 21, 1916. The serologic findings, which had been markedly improved, were again more positive. Finally discharged Aug. 9, 1916. She was given eight or ten further treatments in another city and was reported as doing well, Oct. 22, 1917. All mental symptoms had disappeared and the serologic findings of the spinal fluid were reported negative. (Table 9.)

There is some doubt whether we are here dealing with a pure case of cerebrospinal syphilis or with a case that shows a beginning parenchymatous involvement. As just such cases ought to have the benefit of immediate treatment, we have included her in our series.

CASE 6.—Mary Hitzel, aged 35; housekeeper for father; admitted April 27, 1917. (Table 10.)

Date of Infection.—Chancre in the spring of 1908; well marked secondaries two months later; good and regular treatment with mercury for five years; arsphenamin, one dose in 1915 and two doses in July, 1916. Very intensive treatment in the dispensary of this hospital from Feb. 2, 1917. (See Table 10.)

Life History.—Passed fourth grade of public school. Married in 1907; unhappy marriage; cruel treatment; syphilitic infection derived from husband; divorced in 1910; efficient housekeeper.

Onset of Psychosis.—Began feeling drowsy in 1915; headaches and cramp-like pains in body; November, 1916, had paresthesias over whole left side of body and slight ataxia in arms.

Status on Admission.—Mood unimpaired; no memory defect; retention poor; partial insight; speech stumbling and sticking; both pupils react sluggishly to light; knee and ankle jerks hyperactive; Babinski on right side; hemi-anesthesia of left side of body. For serologic findings see Table 10.

Diagnosis.—General paresis, focal type (early stage).

Progress During Treatment.—Patient's mood continued normal; insight improved; paresthesia and anesthesia disappeared entirely; speech unimproved; neurologic findings unchanged; discharged July 26, 1917. The patient reported several times at the dispensary and was doing quite well, attending to her household duties at home.

The second group is less satisfactory as far as clinical and serologic results are concerned. The case of Mary Olafson (Case 7, Table 11) is typical of the final status. The method of treatment is not typical. In all other cases it was of the usual kind, as outlined. Two cases, Tina Burroughs and Richard Smith (Cases 8 and 9, Table 11), are still undergoing treatment. Charles Green and Samuel Rich (Cases 10 and

11) are at work and doing well. Their sight, decreased to about 20/200 as a result of primary optic atrophy, has not grown worse. Carl Listerman (Case 12), with marked tabes and absolute deafness on account of eight nerve involvement, is doing some work as a huckster and market messenger.

The patients of the third group are clinically and serologically unimproved. John Hogan (Case 13, Table 4), whose serologic chart has been shown, is typical of this group. Harry Blumenstein (Case 14), a clerk, is at work, having been discharged from the hospital with status unchanged. His improvement is probably due to a simple remission.

The last group is very interesting. All these patients have been more or less harmed by the treatment. The status of J. W. Brooks (Case 19), who gradually developed a paraplegia, after the eleventh intraspinous injection, having previously had ten treatments without serious reactions, remains unchanged. Directly after the injection the patient complained of extreme pain. The next day, following a primary retention of urine, incontinence developed and within a week the control of the anal sphincters was also lost. The patient was able to get out of bed and walk a little three or four days after the treatment, but the strength of the muscles of his legs gradually decreased and after a month had elapsed the paraplegia was almost complete. Later, this condition improved somewhat, but he never walked again. The table illustrating his serologic findings has already been shown (Table 3). Ralph Fisher (Case 20) and Sidney McIntosh (Case 21) became incontinent. The former developed this condition after three intraspinous treatments, the latter after the second treatment. Fisher was subsequently given an intraventricular treatment of 25 c.c. of arsphenamized serum. This did not arrest the progressive character of the disease and he died five months after admission to the hospital. McIntosh was treated intravenously six times after the development of bladder symptoms. No clinical or serologic changes resulted. He was sent to a state hospital. Leonard Benson (Case 22) developed a marked arsenic neuritis as has already been stated. Albert Haupt (Case 23) first showed a marked arsenic rash, then nephritic symptoms and finally died of arsenic poisoning seventeen days after the seventh intravenous treatment. The blood picture was that of a typical aplastic anemia with extraordinary leukopenia. The necropsy showed typical liver and kidney degenerations. Both patients were treated with the diarsenol brand of arsphenamin, as was another, not included in this series, who also developed an arsenic rash. John Sudermann (Case 24) died in convulsions six days after an intraspinous treatment. This death is probably due to the convulsion, which in turn is probably a simple manifestation of the disease. On the other hand, the possibility

exists that it can be connected with the treatments. For this reason we have included him in our last group.

It is probable that the poor results obtained with the patients of this last group can be partially overcome by the careful use of arsenic preparations other than the diarsenol brand. No further case of arsenic poisoning has occurred. The danger of motor and sensory root disturbances cannot be entirely avoided, yet this difficulty is outweighed by the excellent results obtained with 25 per cent. of our patients.

Such results would appear worth while. In reviewing the reports of some of the workers in this field, such as those of Fordyce,[16] Ogilvie,[9] Walker and Haller,[17] Draper,[18] Stoner,[19] Byrnes,[10] Cotton,[12] Cutting and Mack,[20] Riggs and Hammes,[21] Tilney,[22] Gaines,[23] Amsden[24] and others, we have found only eight cases of treated general paresis and cerebrospinal syphilis in a total of several hundred, reported serologically negative. Moreover, the majority of these writers believe that it is useless to treat general paresis. We believe that the results obtained by us are due to long-continued intensive treatment, as well as to our special method of application. Furthermore, we believe that every case of general paresis, in the early stages of the disease, ought to be given this "fighting chance" of recovery. We feel absolutely certain that the large percentage of clinical recoveries and the serologic results exclude the possibility of the recoveries being due to simple remissions, in the old sense of the word. We are not certain that our patients will remain in their present state indefinitely; but even if all of them should relapse, we feel that our efforts have not been in vain and that the patients and the community have benefited.

SUMMARY

Twenty-four cases of general paresis, treated according to our method, alternately once a week with arsphenamin serum and mercurialized serum are described.

Six patients were so markedly improved that five of them were able to resume their occupations. All of them gave practically negative serologic findings. The average duration of the present status is fifteen months. We consider these are arrested cases.

16. Fordyce: Jour. Am. Med. Assn., 1917, **68,** 1482.
17. Walker and Haller: THE ARCHIVES INT. MED., 1916, **18,** 376.
18. Draper: Jour. Am. Med. Assn., 1916, **66,** 400.
19. Stoner: Cleveland Med. Jour., 1916, **15,** 238.
20. Cutting and Mack: Jour. Am. Med. Assn., 1914, **62,** 903.
21. Riggs and Hammes: Jour. Am. Med. Assn., 1914, **62,** 1277; Ibid., 1917, **68,** 194.
22. Tilney: Long Island Med. Jour., 1914, **8,** 122.
23. Gaines: Jour. Georgia Med. Assn., 1915 and 1916, **5,** 105.
24. Amsden: Jour. Nerv. and Ment. Dis., 1916, **43,** 265.

Six others were somewhat improved, four resuming their occupations, while two are continuing their treatment. All of these were somewhat improved serologically.

Six showed no clinical or serologic improvement, except in one case. This is undoubtedly a clinical remission; the serologic status remained unchanged.

The last six were harmed by the treatment. One developed a paraplegia; two became incontinent; one died of acute arsenical poisoning and one developed an arsenic neuritis; finally, one died in convulsions, possibly as the result of the treatment.

Whenever the serologic findings tend to become negative, they usually change in the following order and manner:

The cell count is first reduced to normal.

The Wassermann reaction then becomes negative.

The paretic colloidal gold curve changes to an atypical or negative one.

The globulin tests became less marked, but traces of globulin usually remain.

Twenty-three per cent. of all the paretic patients examined in this clinic show negative blood Wassermann reactions.

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